2-Fluoroethylamines. III.[1a] Some Alkylating Agents Derived from Uracil[1b]

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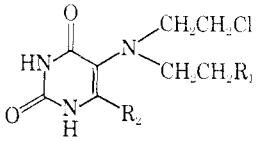
Received July 14, 1967

Uracil mustard (**1**)[2] and dopan (**2**),[3] its 6-methyl homolog, both have demonstrated antitumor activity in animals and are useful in managing some forms of cancer in man.[4,5] Fluoropan (**3**),[6] the fluoro analog of **2**, is reported to have had a dramatic clinical effect in a case of bone cancer. This result suggested that other



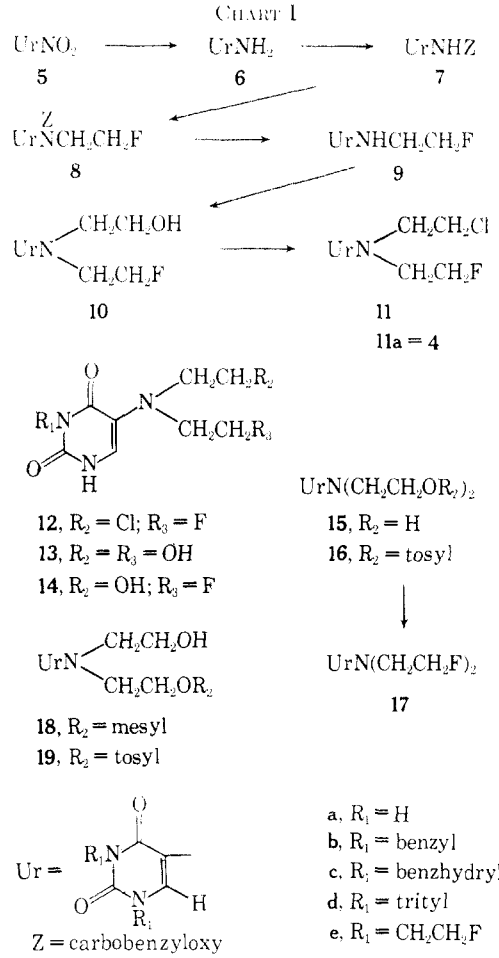
1, R_1 = Cl; R_2 = H
2, R_1 = Cl; R_2 = CH_3
3, R_1 = F; R_2 = CH_3
4, R_1 = F; R_2 = H

fluoro mustards (*i.e.*, those containing a 2-fluoroethylamino group) of uracil be studied.

To provide the closest possible comparison with **3**, we have synthesized and screened **4** together with some other related mustards. Also included are some compounds in which the chlorine of a 2-chloroethylamine has been replaced by a sulfonyloxy group which resembles a halogen atom in some of its chemical properties.[7] The results are reported herein.

For the synthesis of 5-[(2-chloroethyl)(2-fluoroethyl)amino]uracil (**4**) the scheme in Chart I (**5**–**11**) was considered. These conversions have been useful in preparing other chlorofluoro mustards.[1a,8] The use of blocking groups on the pyrimidine nitrogens seemed necessary. The benzyl (series b), benzhydryl (series c), and trityl (series d) were considered to be the potentially most useful blocking groups whose suitability would depend on their stability to reaction conditions and ease of removal in the late stages of the synthesis. Little information is directly available on this point.[9] The scheme in Chart I, which differs from that used by Dubicki, *et al.*,[10] to prepare fluoropan, offered the double advantage that some light may be shed on useful techniques for blocking the uracil nitrogen atoms and that the blocked intermediates might be useful in the synthesis of the bisfluoro mustard, **17**.

CHART I



5
6
7
8
9
10
11
11a = **4**
12, R_2 = Cl; R_3 = F
13, R_2 = R_3 = OH
14, R_2 = OH; R_3 = F
15, R_2 = H
16, R_2 = tosyl
17
18, R_2 = mesyl
19, R_2 = tosyl

a, R_1 = H
b, R_1 = benzyl
c, R_1 = benzhydryl
d, R_1 = trityl
e, R_1 = CH_2CH_2F

1,3-Dibenzyl-5-nitrouracil (**5b**) was readily prepared in good yield by the reaction of benzyl bromide with the disodium salt of 5-nitrouracil in DMF. The nitro group was reduced easily with zinc and ammonium chloride in methanol to afford the amine **6b**. This was converted to the benzyloxycarbonyl derivative, **7b**, whose sodium salt was fluoroethylated to afford the fluoro mustard **8b**. Removal of the benzyloxycarbonyl group with HBr in acetic acid afforded the fluoroethylamine **9b** in high yield, indicating that the benzyl groups were not affected.[9a] Hydroxyethylation followed by treatment with phosphoryl chloride afforded the chlorofluoro mustard **11b**. See Table I for a summary of the physical properties of these compounds.

The benzyl groups on **11b** were not susceptible to hydrogenolysis under mild conditions. More drastic hydrogenolysis conditions were tried, with **10b** as the model; one benzyl group could be removed, but not the second. Likewise, for **15b**, only one benzyl group could be removed. The products appeared to be the 3-benzyl

(1) (a) Paper II: A. P. Martinez, W. W. Lee, and L. Goodman, *J. Med. Chem.*, **8**, 741 (1965). (b) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, U. S. Public Health Service, Contract No. PH-43-64-500. The opinions expressed are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center.

(2) (a) D. A. Lyttle and H. G. Petering, *J. Am. Chem. Soc.*, **80**, 6459 (1958); (b) D. A. Lyttle and H. G. Petering, *J. Nat. Cancer Inst.*, **23**, 153 (1959).

(3) (a) L. F. Larionov, *Brit. J. Cancer*, **10**, 26 (1956); (b) L. F. Larionov and G. N. O. Platonova, *Vop. Onkol.*, **1**, 36 (1955).

(4) H. M. Williams, *Cancer Chemotherapy Rept.*, **32**, 73 (1963).

(5) F. R. White, *ibid.*, **14**, 169 (1961).

(6) L. P. Larionov, M. D. Chadakova, and E. I. Arkhangel'skaia, *Vop. Onkol.*, **7**, 112 (1961); *Cancer Chemotherapy Abstr.*, **2**, 872 (1961).

(7) (a) A. Cohen and R. S. Tipson, *J. Med. Chem.*, **6**, 822 (1963); (b) R. S. Tipson, *Advan. Carbohydrate Chem.*, **8**, 107 (1953).

(8) A. P. Martinez, W. W. Lee, and L. Goodman, *Tetrahedron*, **20**, 2763 (1964).

(9) (a) The benzyl group in 3-benzyl-5-nitrouracil was not removed by HBr–HOAc: see M. Prystas and J. Gut, *Collection Czech. Chem. Commun.*, **28**, 2501 (1963). (b) A. Nováček and D. Hesoun, *ibid.*, **30**, 3890 (1965), successfully removed the benzyl group from 3-benzyl-6-azauracil by hydrogenolysis with Pd–C. (c) Likewise, the benzhydryl group in 3-benzhydryl-6-azauracil and its ribosides was successfully removed by hydrogenolysis at 50° in EtOH over Pd–C by M. Prystas and F. Šorm, *ibid.*, **27**, 1578 (1962), and J. Pliml, M. Prystaš, and F. Šorm, *ibid.*, **28**, 2588 (1963). (d) For other heterocyclic compounds, J. A. Montgomery and H. J. Thomas, *J. Org. Chem.*, **30**, 3235 (1965), have reported that the removal of the 1- or 7-benzyl group from purine was usually slow and difficult, and the benzhydryl group was not significantly better.

(10) H. Dubicki, F. Zielskini, and F. W. Starks, *J. Pharm. Sci.*, **53**, 1422 (1964).

TABLE I
URACIL FLUORO MUSTARDS AND INTERMEDIATES

Compd	Mp, °C	Yield,[a] %	Solvent[b]	Chromatography[c] Solvent	R_f	Formula	Analyses
5b	147.5–148.0	71	M	A	0.91	$C_{18}H_{15}N_3O_4$	C, H, N
5c	91–92	54	A	A	0.93	$C_{30}H_{23}N_3O_4 \cdot 0.2C_7H_8$	C, H, N
5d	139–141	79 (92)	E	*d*		$C_{42}H_{31}N_3O_4 \cdot C_4H_8O_2$	C, H, N
6b	181–183	64	CS	C	0.24	$C_{18}H_{17}N_3O_2 \cdot HCl$	C, H, N
6c	118–120	60	DS	D	0.95	$C_{30}H_{25}N_3O_2 \cdot HCl$	C, H
6d	148–149 (138–140)	(83)	A	E	0.22	$C_{42}H_{33}N_3O_2 \cdot C_2H_6O$	C, N; H[j]
7a	239–240	(29)	A	C	0.41	$C_{12}H_{11}N_3O_4$	C, H
7b	139.0–139.5	61 (79)	DS	A	0.82	$C_{26}H_{23}N_3O_4$	C, H, N
7d	142–143 (135–136)	25 (82)	F	TC	0.61	$C_{50}H_{39}N_3O_4 \cdot C_4H_{10}O$	C, H, N
8b	119.5–120.0	64 (98)	A	A	0.95	$C_{28}H_{26}FN_3O_4$	C, H, F
9a	>300	56	W[e]	B	0.64	$C_6H_8FN_3O_2$	C, H, N, F
9b	188–191	90	*f*	A	0.94	$C_{20}H_{20}FN_3O_2 \cdot HBr$	C, H, N, F
9e	169.5–170.5	(56)	AF	C	0.38	$C_{10}H_{14}F_3N_3O_2 \cdot HBr$	C, H, N; F[k]
10a	164–165 (149–151)	(80)	AE	C	0.67	$C_8H_{12}FN_3O_3$	C, H, N; F[l]
10b	126–128	(90)	DF	C	0.43	$C_{22}H_{24}FN_3O_3 \cdot HCl$	C, H, F
10e	141–142	67	A	C	0.53	$C_{12}H_{18}F_3N_3O_3 \cdot HCl$	C, H, N, F
4	148.5–149.5	50	EP	C	0.40	$C_8H_{11}ClFN_3O_2$	C, H, Cl, F
11b	62.5–63.0	(96)	A	C	0.11	$C_{22}H_{23}ClFN_3O_2$	C, H, Cl, F
13x[g]	165.5–166.0	(21)	C	TM	0.24	$C_{27}H_{27}N_3O_4 \cdot 0.67CHCl_3$	C, H, N, Cl
14b	165–175	81	A	C	0.56	$C_{15}H_{18}FN_3O_3 \cdot HCl$	C, H, F
15b	102–103	(53)	DS			$C_{29}H_{25}N_3O_4$	C, H, N
15d	163.5–164.0	(30)	DS	TE	0.42	$C_{46}H_{41}N_3O_4 \cdot 0.67CH_2Cl_2$	C, H, N, Cl
16a	125–127	19	*f*	TN	0.91	$C_{22}H_{25}N_3O_8S_2$	C, H, N, S
17b	Oil	47	*h*	TC	0.48[i]	$C_{22}H_{23}F_2N_3O_2$	C, H, F
18d	148–149	65 (88)	T	TF	0.36	$C_{47}H_{43}N_3O_6S$	C, H, S
19d	118–119	52	F	TF	0.59	$C_{53}H_{47}N_3O_6S$	C, H, S

[a] Melting points and yields are for analytical samples. Corresponding values enclosed in parentheses are for other samples that are homogeneous, but less purified, and suitable for use in the next step. [b] Solvents used for crystallizations are A, EtOH; C, $CHCl_3$; D, CH_2Cl_2; E, EtOAc; F, Et_2O; M, MeOH; P, petroleum ether 30–60°; S, Skellysolve B; T, toluene; W, H_2O; and CS for $CHCl_3$–Skellysolve B, etc. [c] Chromatography solvent systems are those in ref 14. [d] Decomposed during chromatography. [e] Precipitated from H_2O by adjusting aqueous solution of **9a**·HBr to pH 5 with NH_4OH. [f] Not recrystallized; **9b**·HBr was washed with Et_2O; **16a** was triturated with H_2O and toluene. [g] **13x** Denotes 1-trityl-5-[bis(2-hydroxyethyl)amino]uracil, the N^1 isomer of **13d**. [h] The analytical sample was obtained by thick layer chromatography on a silica gel plate, $CHCl_3$ as solvent. [i] By multiple development under conditions where **16b** had R_f 0.20. [j] H: calcd, 5.98; found, 5.53. [k] F: calcd, 16.5; found, 15.9. [l] F: calcd, 8.75; found, 8.23.

derivatives **14b** and **13b**, for their nmr spectra showed the C-6 proton split into a doublet by coupling with the N-1 proton. On the basis of these results, it seems that the preparation of **4** could not be achieved through the use of benzyl blocking groups.

The benzhydryl series was examined briefly; **5c** and **6c** were prepared in the same way as their benzyl analogs. The benzhydryl series was abandoned when attempts to remove both benzyhydryl groups of **6c** to give **6a** failed.

By using the trityl blocking groups, the sequence **5d** → **6d** → **7d** → **8d** was carried out in a manner similar to the benzyl series. The trityl groups proved to be quite labile. Partial loss of trityl groups occurred when the nitro compound **5d** was heated or recrystallized from methanol; **5d** was more stable in other solvents. For good yields in the reduction of **5d** to **6d**, it was necessary to replace part of the methanol in the solvent mixture with 1,2-dimethoxyethane. The trityl groups on the amine **6d** were less labile; **6d** could be recrystallized from ethanol. When the fluoro mustard **8d** was treated with HBr in acetic acid, all of the blocking groups were removed, and 5-(2-fluoroethylamino)uracil (**9a**) was the product. This was hydroxyethylated to **10a** and treated with phosphoryl chloride to give **4**.

The synthesis of the bisfluoro mustard **17a** was explored without success. All attempts to tosylate 5-[(2-hydroxyethyl)(2-fluoroethyl)amino]uracil (**10a**) failed. 5-(Bishydroxyethyl)aminouracil[2] (**15a**) was readily tosylated to give **16a**, which, however, could not be converted to **17a**. Parallel experiments in the benzyl series demonstrated that the conversion of **15b** through **16b** to **17b** proceeded smoothly. It was apparent that blocking of the uracil ring was necessary. Use of the trityl blocking group posed problems at two points. First, synthesis of the bishydroxyethylamine **15d** was difficult. Hydroxyethylation of **6d** did not take place under the conditions tried. Only a low yield of **15d** could be obtained by the tritylation of **15a**. Second, the bis(2-hydroxyethyl)amine **15d** could be converted only to the monosulfonyloxy derivatives **18d** and **19d**, in contrast to the ready formation of the bistosyloxy derivatives **16a** and **16b**.

A few other 2-fluoroethylamines were prepared. Fluoroethylation of 5-(benzyloxycarbonylamino)uracil (**7a**) afforded the tris(2-fluoroethyl) compound **8e**, an unanalyzed oil which was converted through **9e** to **10e**.

The mustard **4** and a number of the other possible alkylating agents were screened for antitumor activity by the Cancer Chemotherapy National Service Center (CCNSC) according to its protocol.[11] The results were all negative, although **8b** and **9a** caused some reduction in tumor growth in Sarcoma 180, and **16a** caused some increase in survival time in leukemia L1210. The other test systems and compounds tested were Walker 256 subcutaneous (**4**, **17b**), Walker 256 intramuscular

(11) *Cancer Chemotherapy Rept.*, **25**, 1 (1962).

(**16a**), leukemia L1210 (**8b**, **9a**, **19d**, **20d**), Lewis lung carcinoma (**8b**), cell culture against KB cells (**8b**, **9a**, **9b**, **9e**, **10b**, **10e**, and **14b**).

A comparison of **1**–**4** in Walker 256 carcinosarcoma is interesting. Compound **1** is active,[2a] but **4** is not; **2**[10] is more active than **3**.[10] In general, the behavior of the fluoro mustards of uracil follow that reported for other fluoro mustards.[1a,12] Thus, replacement of chlorine by fluorine often led to an increase in toxicity without a corresponding improvement in antitumor activity, at least in the test systems that have been employed.[1a,10,12] These animal test results, in general, stand in contrast to the animal results and the dramatic clinical effect reported for fluoropan.[6,13] It should be noted, however, that the structure reported for fluoropan is under review by Larionov.[13]

Experimental Section[14]

1,3-Disubstituted 5-Nitrouracils (5).—For the preparation of **5b**, this procedure was used. To a stirred mixture of 31.4 g (0.20 mole) of 5-nitrouracil in 400 ml of DMF was added, over a period of 10 min, the NaH (0.5 mole) from 22.4 g of 54% NaH in oil. The oil was removed prior to addition by washing with 150 ml of petroleum ether (bp 30–60°). The mixture, protected from moisture, was heated at 85–90° (bath temperature) and stirred for 3 hr. Benzyl bromide, 100 g (0.58 mole), was added in one portion. After 2 hr of heating and stirring, the solution was evaporated to dryness. The residue was extracted with 700 ml of hot toluene which was evaporated. The syrupy residue was crystallized to afford **5b** (see Table I).

The above procedure was used to prepare **5c** from benzhydryl bromide and **5d** from trityl chloride. Compound **5c** retained toluene even after chromatography on an alumina column followed by crystallization from alcohol (see Table I). Before the crystallization, it was an oil that retained even more toluene.

5-Amino-1,3-disubstituted Uracils (6).—This method was used to prepare **6b**. To a chilled, well-stirred mixture of 16.8 g (50 mmoles) of **5b**, 25 g of NH_4Cl, and 500 ml of absolute MeOH was added 30 g of Zn dust over a 10-min period. The mixture was stirred for 1.5 hr in the cold and 1.5 hr at room temperature, filtered through Celite, and evaporated to dryness. The residue was partitioned between 200 ml of H_2O and 125 ml of $CHCl_3$. The latter was dried, concentrated to *ca.* 100 ml, diluted with 100 ml of Skellysolve B, and treated with anhydrous HCl. The mixture containing crystals was refrigerated for several hours; the white crystals were collected and washed with the solvent to afford **6b**·HCl. This procedure was used to prepare **6c**·HCl and **6d**. For **6d**, the solvent mixture was 1,2-dimethoxyethane–DMF–MeOH (4:2:3), and the reaction was not cooled, although considerable heat was evolved after the Zn addition. Attempts to moderate the reaction gave lower yields of **6d**.

5-(Benzyloxycarbonylamino)-1,3-disubstituted Uracils (7).—For **7b**, the reaction of 2.18 g (7.1 mmoles) of the aminouracil **6b** with 1.50 g (8.8 mmoles) of carbobenzyloxy chloride in 30 ml of CH_2Cl_2 and 5 ml of pyridine by the usual method[8] afforded the product in good yield. In a similar way, **7d** was prepared.

For the preparation of **7a**, a solvent mixture of pyridine and DMSO was used. Even so, about 50% of the starting, insoluble **6a** was recovered. A low yield, 29%, of **7a** was obtained: $\lambda_{max}^{pH\ 1}$ 268 mμ (ε 6740), $\lambda_{max}^{pH\ 7}$ 271 (5940), $\lambda_{max}^{pH\ 13}$ 288 (6740).

5-[N-Benzyloxycarbonyl-N-(2-fluoroethyl)amino]-1,3-disubstituted Uracils (8).—For **8b**, the published procedure[8] employing 11.6 g (26 mmoles) of **7b** and 11.6 g (91.5 mmoles) of 2-bromo-1-fluoroethane afforded the fluoroethylamine product. The same procedure was used to prepare **8d** in 85% yield as a noncrystalline material whose infrared spectrum was free of N–H absorption of the starting material; **8d** was immediately used in the next step without further characterization. The same procedure was used to obtain the tris(2-fluoroethyl)uracil **8e** in 88% yield as a homogeneous oil: R_f 0.30 (solvent A), $\lambda_{max}^{pH\ 1}$ 271 mμ (ε 7160), $\lambda_{max}^{pH\ 7}$ 271 (7120), $\lambda_{max}^{pH\ 13}$ 271 (7070). This was also used immediately in the next reaction.

5-(2-Fluoroethylamino)uracils (9).—For **9a**, a mixture of 8.00 g (10.1 mmoles) of **8d** and 150 ml of 32% HBr in glacial HOAc was stirred for 60 min at room temperature, diluted with 1 l. of Et_2O, and stirred 30 min more. The crystalline precipitate was washed thoroughly with Et_2O and dried to afford **9a**·HBr. This salt was dissolved in H_2O (15 ml/g), filtered, and adjusted to pH 5 with NH_4OH to afford the free base **9a**: $\lambda_{max}^{pH\ 1}$ 260 mμ (ε 6970), 297 (sh, 5180); $\lambda_{max}^{pH\ 7}$ 233 (7750), 292 (5230); $\lambda_{max}^{pH\ 13}$ 292 (8610).

By the above procedure, 1,3-dibenzyl-5-(2-fluroethylamino)-uracil hydrobromide (**9b**·HBr) was obtained from **8b**, analytically pure, after trituration with Et_2O. From **8e**, the tris(2-fluoroethyl)uracil **9e** was obtained in the same way.

5-[(2-Fluoroethyl)(2-hydroxyethyl)amino]uracils (10).—The preparation of **10a** was carried out in the usual manner; 0.77 g (4.9 mmoles) of **9a** and 1.92 g (44 mmoles) of ethylene oxide in 20 ml of glacial HOAc gave, after 22 hr at room temperature, the homogeneous, crystalline product **10a**. Compounds **10b** and **10e** were similarly prepared. For the hydroxyethylation of **6b** to **15b**, the solvent was 90% aqueous HOAc.

5-[(2-Chloroethyl)(2-fluoroethyl)amino]uracils (11).—For the synthesis of **11a**, the HCl salt from 0.30 g (1.38 mmoles) of **10a** was treated with 3.0 ml of $POCl_3$ for 4 hr by the literature procedure[8] to give the product. The same method (reaction time, 30 min) was used to prepare **11b**.

3-Benzyl-5-[(2-fluoroethyl)(2-hydroxyethyl)amino]uracil (14b).—A stirred mixture of 0.50 g (1.15 mmoles) of the dibenzyluracil (**10b**·HCl), 0.5 g of 30% Pd–C, 25 ml of 6 *N* HCl, and 20 ml of 1,2-dimethoxyethane was hydrogenated at 80–84° (1 atm) for 4 hr and at room temperature overnight. The catalyst was removed, and the solution was evaporated. The residue was crystallized to afford **14**: $\lambda_{max}^{pH\ 1}$ 263 mμ (ε 6300); $\lambda_{max}^{pH\ 7}$ 253 (sh, 4920), 300 (sh, 2460); $\lambda_{max}^{pH\ 13}$ 293 (7930); τ 1.87 doublet (C-6 proton, J = 5 cps), 1.80 doublet (N-1 proton, J = 5 cps). Increasing the hydrogenolysis time at 75° to several hours or to 70.3 kg/cm² at 75° did not remove the second blocking group. Refluxing **14** in HBr and glacial HOAc had little effect, as did treatment with Na in liquid NH_3.

Hydrogenolysis of 5-[bis(2-hydroxyethyl)amino]-1,3-dibenzyluracil (**15b**) at room temperature for 3 hr at 1 atm in 2-methoxyethanol with the same catalyst also gave the 3-benzyl derivative **13b**, mp 165–175°, not completely characterized, but whose nmr spectrum also shows the C-6 proton at τ 1.85 as a doublet, J = 3 cps.

Attempted hydrogenolysis of **11b** with Pd–C gave mostly recovered **11b**. With **6c**, neither hydrogenolysis over Pd–C nor treatment with HBr–HOAc could remove the benzhydryl groups completely.

1,3-Ditrityl-5-[bis(2-hydroxyethyl)amino]uracil (15d).—Treatment of 2.15 g (10 mmoles) of 5-[bis(2-hydroxyethyl)amino]-uracil (**15a**) with 20 moles of NaH and 5.58 g (20 mmoles) of trityl chloride in 30 ml of DMF by the procedure used for the preparation of **5d** afforded a mixture that was partitioned between 200 ml of CH_2Cl_2 and 150 ml of H_2O. Concentration of the CH_2Cl_2 layer to 50 ml afforded 1.05 g (21%) of the monotrityl derivative, 1-trityl-5-[bis(2-hydroxyethyl)amino]uracil (**13x**, the N-1 isomer of **13d**). The structure assignment rested on the nmr spectrum which showed the protons on both N-3 (τ 1.00) and C-6 (τ 2.49) as sharp singlets, not coupled with each other. Monoalkylation at N-1 was in accord with previous uracil alkylation results under similar conditions.[15] The mother liquor

(12) (a) G. R. Pettit and R. L. Smith, *Can. J. Chem.*, **42**, 572 (1964); (b) Z. B. Papanastassiou, R. J. Bruni, F. P. Fernandes, and P. L. Levins, *J. Med. Chem.*, **9**, 357 (1966); (c) F. D. Popp, F. P. Silver, and D. W. Alwani, *ibid.*, **10**, 481 (1967).

(13) L. F. Larionov, "Cancer Chemotherapy," Pergamon Press, Oxford, 1965, p 291.

(14) Melting points were determined with the Fisher-Johns apparatus and are not corrected. Paper chromatograms were run by the descending technique on Whatman No. 1 paper except where specified. The solvent systems were A, *n*-BuOH saturated with H_2O; B, C_6H_6–MeOH–H_2O (2:6:1); C, same as B with Schleicher & Schuell No. 2496 acetylated paper; D, 0.1 *N* HCl–EtOH (15:85); E, *t*-BuOH–MeCOEt–HCOOH–H_2O (4:3:1.5:1.5); F, 2 *N* HCl–*i*-PrOH (35:65). Thin layer chromatograms were run on silica gel HF (E. Merck A. G., Darmstadt) in the following solvent systems: TC, $CHCl_3$; TM, MeOH–EtOAc 1:4; TN, same but 1:9; TE, EtOAc–$CHCl_3$ (1:1); TF, same but 1:5. For all chromatograms, the spots were detected visually by ultraviolet light. All evaporations were carried out *in vacuo* with a bath temperature of less than 70°. Anhydrous $MgSO_4$ was used for drying solutions. Skellysolve B is a petroleum fraction with bp 60–68°, essentially *n*-hexane. Celite is a diatomaceous earth product from Johns-Manville. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(15) A. P. Martinez and W. W. Lee, *J. Org. Chem.*, **30**, 317 (1965).

was diluted with an equal volume of petroleum ether, to afford 2.12 g (30%) of the crude **15d** in two crops, mp 161–162 and 158.5–159.5°, identical by infrared spectra and thin layer chromatography. A portion was chromatographed on a thick layer plate of silica gel, developing with EtOAc–$CHCl_3$ (1:1) to afford **15d** that was crystallized once for the analytical sample.

1,3-Dirityl-5-[(2-hydroxyethyl)(2-mesyloxyethyl)amino]uracil (18).—A 1.04-g (9.1 mmoles) portion of $MeSO_2Cl$ was added to a cold (−10°), stirred solution of 2.00 g (2.86 mmoles) of the bishydroxyethylaminouracil **15d**. The solution was stirred for 2 hr at 2°, then partitioned between 200 ml of toluene and 300 ml of H_2O. The organic layer was washed with two 200-ml portions of H_2O, dried, concentrated to *ca.* 20 ml, then diluted with an equal volume of petroleum ether to afford 1.95 g (88%) of **18**.

In a similar way, **19** was prepared from **15d** and *p*-toluenesulfonyl chloride. The same procedure, when applied to **15a** and **15b**, gave the bistosyl derivatives **16a** and **16b**, respectively.

1,3-Dibenzyl-5-[bis(2-fluoroethyl)amino]uracil (17b).—By the literature procedure,[8] a mixture of 5.0 g of anhydrous KF and 5.00 g (7.1 mmoles) of 1,3-dibenzyl-5-[bis(2-tosyloxyethyl)-amino]uracil (**16b**) in 7.5 g of N-methyl-2-pyrrolidone was heated at 160–175° for 40 min to afford 2.69 g (96%) of crude **17b** which was purified by plate chromatography.

Acknowledgment.—We are indebted to Mr. Osborne P. Crews, Jr., and his staff for the large-scale preparation of many intermediates and to Dr. Peter Lim and his staff for the spectra and paper chromatography.

Pyrimidines. XXII. 2,4-Diamino-6-arylamino-5-pyrimidinecarboxaldehydes and Related Compounds[1]

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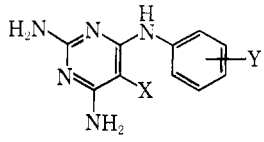
Received September 30, 1967

The synthesis and antitumor evaluation of a number of 2,4-diamino-6-arylaminopyrimidines bearing various functions substituted at position 5 of the pyrimidine moiety (I) have been reported from our laboratories in



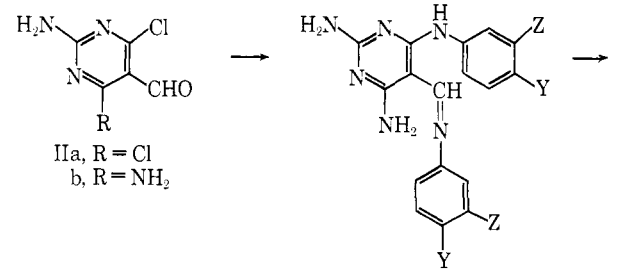
I

recent years.[2–4] Among these compounds, the 6-(halogen-substituted anilino)pyrimidines with a 5-nitroso group demonstrated interesting activity against Adenocarcinoma 755 tumor system.[2] For the retention of biological activity, available information indicates that substitution at position 5 is restricted to a particular size (comparable to −N=O) and its electronic effect (electron withdrawing). This is illustrated by the fact that the corresponding 5-cyano[3] and 5-nitro[4] derivatives possess similar biological activity but the 5-ethyl, 5-bromo, and 5-carbamoyl derivatives were inactive.[3]

As a continuation of this study, synthesis of the corresponding 5-carboxaldehyde derivatives was initiated.

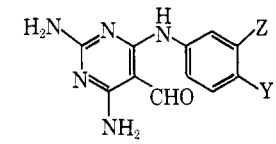
A search in the literature revealed that 5-pyrimidinecarboxaldehydes may be prepared by ozonolysis of ethylenic groups,[5] by hydrolysis of nitromethyl groups,[6] and by proper conversion of cyano,[7] carboxy,[8] trichlorohydroxyethyl,[9] and hydroxymethyl[10] groups. Formyl groups have also been introduced directly by acylation reactions,[11–13] and by the Reimer–Tiemann reaction.[14] Recently, it was reported by Klötzer and Herberz that 2-amino-4,6-dichloro-5-pyrimidinecarboxaldehyde (IIa) was prepared in good yield from 2-amino-4,6-pyrimidinediol by a modified Vilsmeier–Haack synthesis.[15,16] This material was therefore used as the starting material for the present investigation.

When IIa was stirred with ethanolic ammonia at room temperature, 2,4-diamino-6-chloro-5-pyrimidinecarboxaldehyde (IIb) was obtained in good yield. Treatment of the intermediate IIb with 2 equiv of a substituted aniline in refluxing ethanol yielded the anils of 2,4-diamino-6-(substituted anilino)-5-pyrimidine-carboxaldehyde (III), with characteristic ultraviolet absorption maxima in the 350–360-mμ region at pH 1 and 11. The desired 2,4-diamino-6-(substituted anilino)-5-pyrimidinecarboxaldehydes (IV) were readily obtained by acid hydrolysis of III in 0.1 *N* HCl. These products do not possess any ultraviolet absorption maxima above 340 mμ in either pH 1 and 11.



IIa, R = Cl
b, R = NH_2

III



IV

These 5-pyrimidinecarboxaldehydes (IV) displayed no significant anticancer activity against leukemia L1210 and Walker carcinosarcoma 256.

(1) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract PH-43-65-94.

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