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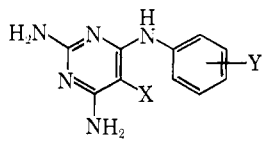
The synthesis and antitumor evaluation of a number of 2,4-diamino-6-arylaminopyrimidines bearing various functions substituted at position 5 of the pyrimidine moiety (I) have been reported from our laboratories in



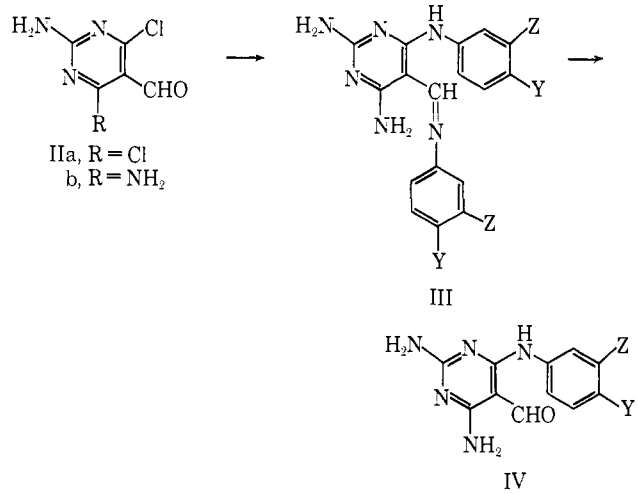
I

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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Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.3% of the theoretical values.

2,4-Diamino-6-chloro-5-pyrimidinecarboxaldehyde (IIb).—A suspension of 5.76 g (0.03 mole) of finely powdered 2-amino-4,6-dichloro-5-pyrimidinecarboxaldehyde[15] (IIa) in 250 ml of ethanolic NH_3 (prepared by saturating dry NH_3 in absolute EtOH at 5°) was stirred at room temperature for 18 hr. The resulting white precipitate was filtered off, washed (H_2O, cold EtOH), and dried at 80°. It was recrystallized from EtOH to give 4.3 g (83% yield) of analytically pure product which decomposed at 240° upon rapid heating: $\lambda_{max}^{pH\ 1}$ 264 mμ (ε 10,800), 305 (16,500); $\lambda_{max}^{pH\ 13}$ 264 mμ (ε 11,000), 303 (18,500). *Anal.* ($C_5H_5ClN_4O$) C, H, N.

2,4-Diamino-5-[N-(*p*-bromophenyl)formimidoyl]-6-(*p*-bromoanilino)pyrimidine (III, Y = Br, Z = H).—A mixture of 8.6 g (0.05 mole) of IIb and 25.8 g (0.15 mole) of *p*-bromoaniline was refluxed in 250 ml of EtOH containing 1 ml of concentrated HCl. A yellow solid gradually precipitated from the refluxing solution. After 3 hr the solid was filtered off from the boiling reaction mixture, triturated with Na_2CO_3 solution, filtered, washed well with H_2O, and finally recrystallized from a large volume of EtOH (1 g/1000 ml) to yield 13.6 g (59% yield); mp 269–272° dec; $\lambda_{max}^{pH\ 1}$ 269 mμ (ε 32,300) and 364 (12,900); $\lambda_{max}^{pH\ 13}$ 234 mμ (ε 18,000), 278 (24,000), and 362 (18,300). *Anal.* ($C_{15}H_{11}Br_2N_5$) C, H, N.

The following compounds have also been similarly prepared: their uv absorption bands were as expected. 2,4-Diamino-5-[N-(*p*-tolyl)formimidoyl]-6-(*p*-tolnidino)pyrimidine (III, Y = CH_3; Z = H), 73% yield, mp 130–135° dec. *Anal.* ($C_{19}H_{20}N_6 \cdot HCl \cdot H_2O$) C, H, N. 2,4-Diamino-5-[N-(*p*-iodophenyl)formimidoyl]-6-(*p*-iodoanilino)pyrimidine (III, Y = I; Z = H), 66% yield, mp 257–258° dec. *Anal.* ($C_{17}H_{14}I_2N_6$) C, H, N. 2,4-Diamino-5-[N-(3,4-dichlorophenyl)formimidoyl]-6-(3,4-dichloroanilino)pyrimidine (III, Y, Z = Cl), 86% yield, mp 304–306° dec. *Anal.* ($C_{17}H_{12}Cl_4N_6 \cdot HCl$) C, H, N.

2,4-Diamino-6-(*p*-bromoanilino)-5-pyrimidinecarboxaldehyde (IV, Y = Br; Z = H).—A suspension of 5 g of III (Y = Br; Z = H) in 1000 ml of 0.1 *N* HCl was refluxed for 3 hr. The resulting solution, which still contained a small amount of insoluble material, was treated with decolorizing charcoal and filtered. The pH of the filtrate was brought to 8–9 by the careful addition of $NaHCO_3$, and the precipitated product was collected by filtration. It was washed (cold H_2O) and recrystallized from EtOH–H_2O to give 2.04 g (61% yield) of analytically pure product: mp 210–215°; $\lambda_{max}^{pH\ 1}$ 268 mμ (ε 38,800); $\lambda_{max}^{pH\ 13}$ 265 mμ (ε 30,500), 296 (17,200). *Anal.* ($C_{11}H_{10}BrN_5O$) C, H, N.

The following 5-pyrimidinecarboxaldehydes have also been similarly prepared. Their uv absorption bands were as expected. 2,4-Diamino-6-(*p*-tolnidino)-5-pyrimidinecarboxaldehyde (IV, Y = CH_3; Z = H), 46% yield, mp 221–224°. *Anal.* ($C_{12}H_{13}N_5O$) C, H, N. 2,4-Diamino-6-(3,4-xylidino)-5-pyrimidinecarboxaldehyde (IV, Y, Z = CH_3) was obtained directly from IIb and 3,4-xylidine in 32% yield, mp 215–218°. *Anal.* ($C_{13}H_{15}N_5O$) C, H, N. 2,4-Diamino-6-(*p*-iodoanilino)-5-pyrimidinecarboxaldehyde (IV, Y = I; Z = H), 41% yield, mp 228–230°. *Anal.* ($C_{11}H_{10}IN_5O$) C, H, N.

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Substituted 7,8,9,10-Tetrahydro-6H-cyclohepta[*b*]quinolines

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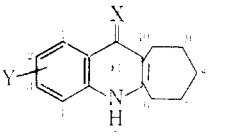
Recently a number of 4-N-substituted amino- and carbamoyl-2,3-polymethylenequinolines were synthesized and found to exhibit a wide spectrum of pharmacological properties.[1] An earlier report described the analeptic activity of aminocycloheptaquinoline.[2] In the present communication the synthesis of 11-substituted 7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinolines and the evaluation of these compounds for antidepressant activity is described.

7,8,9,10-Tetrahydro-6H-cyclohepta[*b*]quinolin-11-ones (Ia–i) (Table I) were prepared by refluxing

TABLE I

7,8,9,10-TETRAHYDRO-6H-CYCLOHEPTA[*b*]QUINOLIN-11-ONES AND -11-THIONES



Compd	X	Y	Mp, °C	Yield, %[c]	Recrystn solvent[d]	Formula[e]
Ia[a]	O	H	330 dec	82[c]	A	$C_{14}H_{13}NO$
Ib[b]	O	2-Cl	380 dec	78[c]	A	$C_{14}H_{12}ClNO$
Ic[b]	O	3-Cl	390 dec	60[c]	A	$C_{14}H_{12}ClNO$
Id[b]	O	4-Cl	271 dec	50	A	$C_{14}H_{12}ClNO$
Ie	O	3-OCH_3	314 dec	28	A	$C_{15}H_{15}NO_2$
If	O	3-NO_2	355 dec	90[c]	B	$C_{14}H_{12}N_2O_3$
Ig	O	3-CF_3	355 dec	84[c]	A	$C_{15}H_{12}F_3NO$
Ih	O	2,4-Cl_2	281–283	15	A	$C_{14}H_{11}Cl_2NO$
Ii	O	2,3,4-$(OCH_3)_3$	253 dec	17	A	$C_{17}H_{19}NO_4$
IIa	S	H	218–220	59	C	$C_{14}H_{13}NS$
IIb	S	2-Cl	250–252	60	C	$C_{14}H_{12}ClNS$
IIc	S	3-Cl	258–260	80	C	$C_{14}H_{12}ClNS$

[a] Reference 3. [b] These compounds are described by M. V. Sigal, Jr., B. J. Breid, and P. Marchini, U. S. Patent 3,232,945 (1966); *Chem. Abstr.*, **64**, 14174 (1966), by condensing *p*-chloro-, *m*-chloro-, and *o*-chloroaniline with 2-carbethoxycycloheptanone with melting points of 360, 360, and 264–265°, respectively. [c] Crude yield. [d] A = ethanol, B = DMF, and C = pyridine–water. [e] All compounds were analyzed for C, H, N. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.3% of the theoretical values.

o-aminobenzoic acid and substituted *o*-aminobenzoic acids with cycloheptanone in xylene while removing water azeotropically. Using this procedure the yields were much higher than those obtained on heating the two reactants without solvent[3] and, in many cases, the crude products could be used for subsequent reactions without further purification. 7,8,9,10-Tetrahydro-6H-cyclohepta[*b*]quinoline-11-thiones (IIa–c) (Table I) were obtained by reaction of 7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinolin-11-ones (Ia–c) with phosphorus pentasulfide in pyridine (Scheme I). Alkylation of 7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinolin-11-ones (Ia–i) with dialkylaminoalkyl halides in dimethylformamide and sodium hydride yielded 11-dialkylaminoalkoxy-7,8,9,10-tetrahydro-6H-cyclohepta[*b*]-quinolines (IIIa–o) (Table II). Similar treatment of IIa–c with dialkylaminoalkyl halides gave 11-dialkylaminoalkylthio derivatives (IVa–g). 7,8,9,10-Tetrahydro-6H-cyclohepta[*b*]quinolin-11-ones (Ia–c) were converted to 11-chloro-7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinolines (Va–c) with phosphorus oxychloride.[1] Compounds Va–c were condensed with dialkyl-

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