pure sample as colorless plates; m.p. 65–65.5°, ν_{max}^{KBr} 1734, 1087, and 1063 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{13}NO_4S$: C, 51.77; H, 5.09; N, 5.49; S, 12.55. Found: C, 51.71; H, 4.86; N, 5.50; S, 12.54.

2,2′-Methylenebis(1,1,3-trioxo-benzo[*d*]isothiazoline) (VIII).—A solution composed of saccharin (3.3 g.), paraformaldehyde (0.6 g.), concd. hydrochloric acid (0.2 ml.), and acetic acid (20 ml.) was heated at steam bath temperature for 10 hr. After the first 3-hr. period, 0.3 g. of paraformaldehyde was added to the mixture. The crystalline product (VIII, 0.6 g.), m.p. 285–289°, which formed as the reaction progressed, was collected by filtration. Mixture melting point determination and infrared spectral comparison, in potassium bromide, with an authentic specimen (m.p. 286–289°) of methylenebisisothiazoline[13] (VIII) confirmed the identical nature of both substances.

In a prior experiment, essentially the same yield of product (VIII) was obtained when the reaction mixture also contained bis(2-chloroethyl)amine hydrochloride (3.3 g.). Under these conditions the amine was converted to its *N*-methyl derivative (see below).

***N*-Methylbis(2-chloroethyl)amine (IX) perchlorate.**—A solution of bis(2-chloroethyl)amine hydrochloride[17] (1.1 g.) and paraformaldehyde (0.2 g.) in glacial acetic acid (4 ml.) was heated overnight at steam bath temperature. The mixture was then concentrated *in vacuo* to a mobile oil and diluted with cold water (3 ml.) followed by 70% perchloric acid (2 ml.). The crystalline product (IX perchlorate) which separated weighed 1.1 g. (76%) and melted at 95–98°. Two recrystallizations from ethanol afforded a pure specimen as colorless leaflets, m.p. 106–107°. The perchlorate was added to cold 10% aqueous sodium hydroxide and the liberated amine was extracted with ether. Hydrogen chloride was conducted into the dry (magnesium sulfate) ethereal extract and the hydrochloride derivative of IX was collected. An analytical sample crystallized from acetone as colorless plates melting at 110–110.5° (lit.,[21] m.p. 108–110°).

Anal. Calcd. for $C_5H_{12}Cl_3N$: C, 31.19; H, 6.28; Cl, 55.26; N. 7.28. Found: C, 31.37; H, 6.74; Cl, 54.94; N, 7.08.

The hydrochloride was identical[19] with a commercial sample (Bios Laboratories) of *N*-methylbis(2-chloroethyl)-amine hydrochloride (m.p. 110°).

(21) M. Ishidate and S. Tsukagoshi, *Chem. Pharm. Bull.* (Tokyo), **8**, 87 (1960).

Potential Anticancer Agents.[1] LXXI. Some Diaminopyrimidines and Diamino-*s*-triazines Related to Daraprim

KAREN A. HYDE, EDWARD M. ACTON,[2a] B. R. BAKER,[2b] AND LEON GOODMAN

Life Sciences Division, Stanford Research Institute, Menlo Park, Calif.

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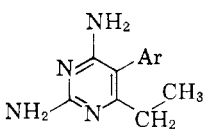
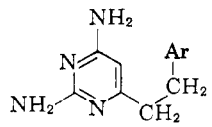
2,4-Diamino-6-phenethylpyrimidines (II) were formed by condensation of 5-aryl-3-ketovalerates with guanidine carbonate to afford 2-amino-4-hydroxy-6-phenethylpyrimidines, which were chlorinated and aminated. 2,4-Diamino-6-phenethyltriazines (III) formed on condensation of biguanide with hydrocinnamates. Ring-halogenated hydrocinnamic acids were common intermediates to II and III. 2,4-Diamino-6-styryltriazines (XVIII) were obtained from 2,4-diamino-6-methyltriazine and halobenzaldehydes in concentrated sulfuric acid.

An earlier paper[3] in this series described the synthesis of nitrogen mustards derived from Daraprim (I) and from a related diaminodihydro-*s*-triazine. Study of further structural modifications of Daraprim was prompted by a continuing interest in these diamino heterocycles, which function in a variety of systems as folic acid antagonists like the structurally related drug, Amethopterin; the latter is clinically useful against cancer. In particular it was of interest to see what biological effect, if any, would result by transferring the 5-aryl group of I to the 6-ethyl group, to form the 6-phenethyl derivatives (II). At the same time, study of similarly substituted triazines (III)[4] would be permitted by their easy synthesis from intermediates required for preparing II.

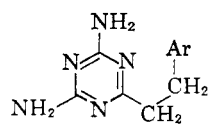
In devising a synthetic scheme for II, it appeared that a series of ring-halogenated hydrocinnamic acids could serve as precursors to both II and III. Condensation of β-ketocarboxylic



I. Ar = *p*-ClC_6H_4



IIa. Ar = C_6H_5
b. Ar = *p*-FC_6H_4
e. Ar = *m,p*-$Cl_2C_6H_3$



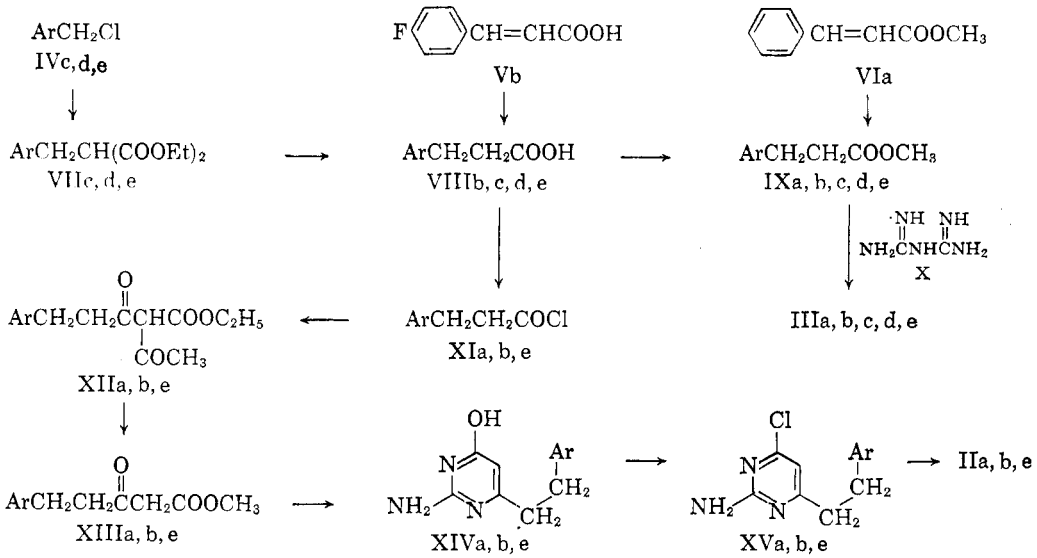
IIIa. Ar = C_6H_5
b. Ar = *p*-FC_6H_4
c. Ar = *p*-ClC_6H_4
d. Ar = *o*-ClC_6H_4
e. Ar = *m,p*-$Cl_2C_6H_3$

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series, see B. Weinstein, O. P. Crews, M. A. Leaffer, B. R. Baker, and L. Goodman, *J. Org. Chem.*, **27**, 1389 (1962).

(2) (a) To whom reprint requests should be addressed; (b) Present address: School of Pharmacy, University of Buffalo, Buffalo, N. Y.

(3) J. I. DeGraw, L. O. Ross, L. Goodman, and B. R. Baker, *J. Org. Chem.*, **26**, 1933 (1961).

(4) For summary of antifolic activity and antitumor properties of related dihydrotriazines, see E. J. Modest in *Heterocyclic Compounds*, Vol. 7, ed. by R. C. Elderfield, John Wiley and Sons, Inc., New York, 1961, p. 717.



esters with guanidine[5] constitutes a smooth synthesis of 2-amino-4-hydroxy-6-alkylpyrimidines; these are easily converted to 2,4-diaminopyrimidines such as II by replacement with chlorine at the 4-position and amination. Ring-halogenated hydrocinnamoyl chlorides, on acylation of acetoacetic ester and cleavage of the acetyl group, would lead to the required β-keto esters with the appropriate phenethyl tail for forming II. A well established synthesis of 2,4-diamino-6-alkyl-*s*-triazines involves the condensation[6] of carboxylic esters with biguanide (X). Use of the corresponding ring-halogenated hydrocinnamic esters would provide the desired 6-phenethyl groups of III. Successful syntheses of II and III have been based on these methods (Scheme I). Halogen substituents of the benzene ring in II were limited to *p*-fluoro and *m,p*-dichloro; *p*-fluoro, *o*- and *p*-chloro, and *m,p*-dichloro derivatives of the parent triazine IIIa were prepared. *m,p*-Dichloro compounds were of special interest because in similar pyrimidines and triazines previously tested the antitumor activity and often other biological effects were greater than in the analogous *p*-chloro compounds.[7] These considerations prompted the preparation of IIe rather than the *p*-chloro analog which is related to Daraprim (I).

The hydrocinnamic acids VIII were best prepared on a moderately large scale by alkylation[8] of malonic ester with the appropriate halobenzyl chlorides IVc, d, e, followed by acidic hydrolysis and decarboxylation of the resulting benzylmalonic esters VIIc,d,e in a single step[8] to form VIIIc,d,e. The *p*-fluoro acid VIIIb was prepared by hydrogenation of *p*-fluorocinnamic acid (Vb), obtained from *p*-fluorobenzaldehyde by the Doebner modification[9] of the Perkin reaction, at one atmosphere in glacial acetic acid with palladium. For preparation of the triazines III, the acids VIIIb,c,d,e were converted to the corresponding methyl esters IXb,c,d,e. Although analytical data for IXc and IXd were unsatisfactory, gas-liquid partition chromatography indicated that the esters were 100.0 and 99.7% pure, respectively. A sample of IXc for comparison, identical in infrared absorption but slightly less in purity (97%),

SCHEME I

Series	a	b	c	d	e
Ar	C_6H_5	*p*-FC_6H_4	*p*-ClC_6H_4	*o*-ClC_6H_4	*m,p*-$Cl_2C_6H_3$

was prepared by hydrogenation of methyl *o*-chlorocinnamate in benzene at one atmosphere. This was possible with strongly prereduced palladium black[10] as catalyst; with platinum oxide, as described for hydrogenation of 2,4-dichlorocinnamic acid,[11] up to 15% of the chlorine was lost by hydrogenolysis. Reduction of methyl cinnamate (VIa) with ordinary palladium-on-carbon as catalyst was the method of choice for the parent ester IXa. The methyl hydrocinnamates were condensed with biguanide in methanol solution[12] at room temperature to form IIIa,b,c,d,e (Table III). Over-all yields from IV were 11–22%.

Conversion of the hydrocinnamic acids VIIIb,e to acid chlorides XIb,e was the first step toward synthesis of the pyrimidines II. Acylation of

(5) E. A. Falco, P. B. Russell, and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3753 (1951).

(6) For review and leading references, see E. M. Smolin and L. Rapoport, "*s*-Triazines and Derivatives," Interscience Publishers, Inc., New York, 1959, pp. 226–229; E. J. Modest, ref. 4, p. 663.

(7) A. Goldin, J. M. Venditti, S. R. Humphreys, and N. Mantel, *J. Natl. Cancer Inst.*, **21**, 495 (1958); see discussion in G. H. Hitchings, E. A. Falco, H. VanderWerff, P. B. Russell, and G. B. Elion, *J. Biol. Chem.*, **199**, 43 (1952).

(8) R. A. Barnes and L. Gordon, *J. Am. Chem. Soc.*, **71**, 2644 (1949).

(9) J. R. Johnson, *Org. Reactions*, **I**, 249 (1942).

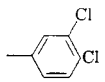
(10) K. Kindler, H.-G. Helling, and E. Sussner, *Ann.*, **605**, 200 (1957).

(11) E. R. Andrews, M. G. Van Campen, and E. L. Schumann, *J. Am. Chem. Soc.*, **75**, 4003 (1953).

(12) C. G. Overberger, F. W. Michelotti, and P. M. Carabateas, *J. Am. Chem. Soc.*, **79**, 941 (1957); J. T. Shaw and F. J. Gross, *J. Org. Chem.*, **24**, 1809 (1959); J. T. Thurston, U. S. Patent 2,461,943, *Chem. Abstr.*, **43**, 3854f (1949).

TABLE I

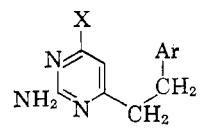
5-ARYL-3-KETOVALERIC ESTERS

Compound	Ar	B.P. (mm.)	% Yield[b]	% By-product $ArCH_2CH_2$-COOR[b]	Formula	Calcd., % (Found, %) C	H	F
XIIIa		120–124 (2)	52[c]	16[f]	$C_{12}H_{14}O_3$			
XIIIb		106–114 (2)	57[c]	18[f]	$C_{12}H_{13}FO_3$· $C_{13}H_{15}FO_3$	64.9[g] (65.0)	6.10[g] (6.02)	8.23[g] (8.29)
XIIIe		44–45[e]	39[d]	25[c]	$C_{12}H_{12}Cl_2O_3$	52.4 (52.6)	4.40 (4.11)	17.4[h] (17.6[h])

[a] From XI by procedure of Doherty[13]; intermediate diketo esters (XII, 92–96% crude yields) not distilled or purified. [b] Calcd. as R = CH_3, based on acid chloride. [c] Isolated by extraction, then distillation. [d] Isolated as solid on chilling oily product. [e] M.p., analytical sample, recrystallized from aqueous methanol. [f] Distillation forerun. [g] Calcd. for R = 50% CH_3, 50% C_2H_5; a sample from another run showed R = 100% C_2H_5. [h] % O.

TABLE II

2-AMINO-6-ARYLETHYL-4-SUBSTITUTED PYRIMIDINES



Compound	X	Ar	M.P.[a]	% Yield	Formula	Calcd., % (Found, %) C	H	N	Cl
XIVa	OH	C_6H_5	240–250[c]	73[i,c]	$C_{12}H_{12}N_2O$	67.0 (66.9)	6.09 (5.98)	19.5 (19.5)	... ...
XIVb	OH	C_6H_4F-*p*	250–253, remelts 265–266[d]	86[i,b]	$C_{12}H_{11}FN_2O$	61.8 (61.8)	5.19 (5.37)	18.0 (17.9)	8.14[k] (8.38)[k]
XIVe	OH	$C_6H_3Cl_2$-*m,p*	261–264[b]	75[i,f]	$C_{12}H_{10}Cl_2N_2O$	50.7 (50.7)	3.90 (4.04)	14.8 (15.1)	25.0 (24.9)
XVa	Cl	C_6H_5	90–91[g]	68[h]	$C_{12}H_{11}ClN_2$	61.7 (61.4)	5.18 (5.31)	18.0 (17.9)	15.2 (15.0)
XVb	Cl	C_6H_4F-*p*	119–120[g]	68[h]	$C_{12}H_{10}ClFN_2$[l]	57.2 (57.2)	4.41 (4.25)	16.7 (16.5)	14.1 (14.1)
XVe	Cl	$C_6H_3Cl_2$-*m,p*	170–172[g]	89[h]	$C_{12}H_9Cl_3N_2$	47.6 (47.4)	3.33 (3.39)	13.9 (13.9)	13.2 (13.4)
IIa	NH_2	C_6H_5	132–134[e]	54[e]	$C_{12}H_{13}N_3$	67.3 (67.5)	6.59 (6.59)	26.2 (26.0)	... ...
IIb	NH_2	C_6H_4F-*p*	212–213[d]	88[h]	$C_{12}H_{12}FN_3$	62.1 (62.2)	5.64 (5.82)	24.1 (24.0)	... ...
IIe	NH_2	$C_6H_3Cl_2$-*m,p*	171–172[e,j]	73[e]	$C_{12}H_{11}Cl_2N_3$	50.9 (51.0)	4.27 (4.36)	19.8 (19.7)	25.0 (25.3)

[a] Of analytical sample. Recrystallization solvents were: [b] methanol, [c] methanol–water, [d] ethanol, [e] ethanol–water, [f] 2-methoxyethanol, [g] dichloromethane–petroleum ether. [h] Not recrystallized. [i] Based on XIII as methyl ester. [j] Mixed melting point with XVe, 150–157°. [k] % F. [l] % F: Calcd., 7.55; Found, 7.40.

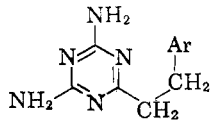
ethyl acetoacetate[13] was carried out in ether with magnesium ethoxide as base. The resulting diketo esters XIIa,b,e, without purification, were cleaved in methanolic sodium methoxide,[13] with preferential loss of the acetyl group in each case to form 40–60% over-all yields of the 5-aryl-3-ketovalerates XIIIa,b,e (Table I). In this step, equilibration of the carboxylate group of XII with the medium to result in the methyl esters XIII was expected; analyses suggested that though methyl esters were generally obtained, either methyl or ethyl esters were possible. Both have been previously reported[13,14] for such products. Appreciable amounts of the hydrocinnamates IX were also recovered along with the keto esters XIII; these can have resulted from the alternative cleavage of XII to regenerate acetoacetic ester, or can have originated in the previous acylation step by a side reaction of XI with magnesium ethoxide. Condensation of the keto esters XIIIa,b,e with guanidine carbonate occurred in refluxing methanol,[5] forming the 2-amino-4-hydroxy-6-phenethylpyrimidines (XIVa,b,e; Table II). Replacement of the 4-hydroxyl by chlorination in refluxing phosphoryl chloride afforded XVa,b, and e as hydrochloride salts, regenerated with aqueous ammonia at *p*H 8 (Table II). The desired 2,4-diamino compounds IIa,b,e (Table II)

(13) D. G. Doherty, *J. Am. Chem. Soc.*, **77**, 4887 (1955).

(14) S. B. Soloway and F. B. LaForge, *J. Am. Chem. Soc.*, **69**, 2677 (1947).

TABLE III

2,4-DIAMINO-6-ARYLETHYL-s-TRIAZINES

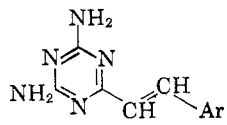


Compound	Ar	M.P.,[a,b] °C.	% Yield	Method	λ_{max} mμ (ε)[d]	Formula	Calcd., % (Found, %) C	H	N	Cl
IIIa		185–187	52[b]	A	258 (3540)	$C_{11}H_{13}N_5$	61.4	6.09	32.5	
			92[b]	B			(61.4)	(6.15)	(32.8)	
IIIb		223–224	52[b]	A	258 (4040)	$C_{11}H_{12}FN_5$	56.6	5.19	30.0	8.15[e]
			74[c]	B	272 (1830)		(56.9)	(5.29)	(30.1)	(8.32)[e]
IIIc		213–214	46[b]	A	256 (3470)	$C_{11}H_{12}ClN_5$	52.9	4.85	28.1	14.2
					276 (570)[f]		(53.1)	(5.26)	(27.9)	(14.0)
IIId		182–183	51[b]	A	256 (3900)	$C_{11}H_{12}ClN_5$	52.9	4.85	28.1	14.2
							(52.8)	(4.99)	(27.9)	(14.0)
IIIe		189–190	71[c]	A	257 (3430)	$C_{11}H_{11}Cl_2N_5$	46.5	3.90	24.7	25.0
					282 (470)		(46.4)	(3.93)	(24.6)	(25.2)

[a] Of analytical sample. [b] Recrystallized from methanol. [c] Not recrystallized. [d] In methanol. [e] % F. [f] Shoulder.

TABLE IV

2,4-DIAMINO-6-STYRYL-s-TRIAZINES



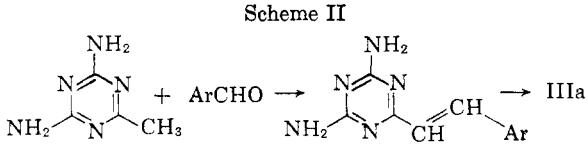
Compound	Ar	M.P.[a] °C.	% Yield	λ_{max} mμ (ε)[h]	Formula	Calcd., % (Found, %) C	H	N	Cl
XVIIIa		275–277[e]	61[e]	297 (26,200)	$C_{11}H_{11}N_5$	61.9	5.20	32.9	...
						(61.9)	(5.11)	(32.8)	...
XVIIIb		280–286[c]	60[d]	292 (27,600)	$C_{11}H_{10}FN_5$	57.1	4.36	30.3	8.22[g]
		290–295[f]				(57.2)	(4.26)	(30.0)	(8.23)[g]
						(57.3)	(4.29)	(30.2)	(8.32)[g]
XVIIIc		270–275[d]	50[d]	297 (31,200)	$C_{11}H_{10}ClN_5$	53.3	4.07	28.3	14.3
						(53.2)	(4.22)	(28.4)	(14.3)
XVIIId		265–270[b]	53[d]	288 (24,000)	$C_{11}H_{10}ClN_5$	53.3	4.07	28.3	14.3
						(53.3)	(4.18)	(28.4)	(14.1)
XVIIIf		264–269[c]	62[e]	292 (28,200)	$C_{11}H_9Cl_2N_5$	46.8	3.22	24.8	25.1
						(46.7)	(3.48)	(24.8)	(25.0)

[a] Of analytical sample. Recrystallized from [b] methanol (1 g./200 ml.), [c] ethanol, [d] 2-methoxyethanol, [e] 2-methoxyethanol–water. [f] Sublimed. [g] % F. [h] In methanol.

were obtained by amination with ethanolic ammonia in a sealed bomb. Over-all yields from VIII were 15–24%.

Modification of 2,4-diamino-6-methyltriazine (XVI, Scheme II) was tempting as an alternative approach toward III, especially since XVI is commercially available. Condensation of XVI with a series of halobenzaldehydes XVIIa,b,c,d,f occurred smoothly in hot concentrated sulfuric acid[15] to form a series of 2,4-diamino-6-halostyryltriazines (XVIIIa,b,c,d,f; Table IV). Use of hot concentrated hydrochloric acid as described[16] for the more reactive *p*-dimethylaminobenzaldehyde led to only low yields of the styryl compounds. Partial loss of halogen prevented successful hydrogenation of the halostyryltriazines. Hydrogenation of the *p*-chloro analog XVIIIc at one atmosphere with 5% palladium-on-carbon formed a mixture of the

Scheme II



XVI XVII XVIII

Series a,b,c,d, same as Scheme I
Series f, Ar = *o*,*p*-$Cl_2C_6H_3$

(15) v. Humnicki, *Chem. Zentr.*, **78**, 706 (1907).

(16) N. V. Khromov-Borisov and E. V. Kisareva, *Zhur. Obshchei Khim.*, **29**, 3010 (1959).

desired IIIc and the nonhalogenated phenethyltriazine (IIIa). The *p*-fluorostyryltriazine (XVIIIb) was more resistant to hydrogenolyis under the same conditions. On a small-scale (0.25 g.) hydrogenation, an analytically pure sample of IIIb was obtained, identical in melting point, infrared spectrum, and paper chromatography to IIIb from IXb and X (Scheme I). However, material of equal purity could not be obtained on a larger scale. Reduction of the parent styryltriazine (XVIIIa) to IIIa was straightforward, but was only in small runs as convenient as the synthesis from VIa *via* IXa. Brief attempts to prepare 6-styrylpyrimidines from 2,4-diamino-6-methylpyrimidine (or the diacetyl derivative) as in Scheme II, with formic acid and with acetic anhydride as condensing agents, afforded only unchanged starting material. The 6-methyl group of the diaminopyrimidine has been shown[16] to be less reactive than that of XVI.

Experimental[17]

Benzylmalonic Esters.—The *p*-chloro[18] (VIIc) and *o*-chloro[8,19] (VIId) isomers were prepared as in ref. 8, and the *m*,-*p*-dichloro isomer VIIe by the Leuchs procedure.[20] Yields were 50–60%.

The distillation residue from VIIe afforded 25% of the dialkylation product, m.p. 96°, after ethanol recrystallization.

Anal. Calcd. for $C_{21}H_{20}Cl_4O_4$: Cl, 29.7. Found: Cl, 29.7.

Chlorinated Hydrocinnamic Acids.—The *p*-chloro[10] (VIIIc), *o*-chloro[8,21] (VIIId), and *m*,*p*-dichloro[22] (VIIIe, m.p. 95–96°, lit. 71°) acids were prepared in 55–85% yields as in ref. 8.

Anal. Calcd. for $C_9H_8Cl_2O_2$: C, 49.3; H, 3.68; Cl, 32.4. Found: C, 49.3; H, 3.95; Cl, 32.3.

***p*-Fluorohydrocinnamic Acid (VIIIb).**[23]—*p*-Fluorobenzaldehyde was converted to *p*-fluorocinnamic acid (Vb) by the Doebner modification of the Perkin reaction[9] in 75% yield, m.p. 200–202° (lit.[24] 202°). This acid in glacial acetic acid solution (1 g. per 30–35 ml.) was hydrogenated at 1 atm. with 5% palladium-on-carbon catalyst (1 g. per 13 g. of compound). Hydrogen uptake ceased abruptly after consumption of 1 molar equivalent. The product was obtained after removal of acetic acid *in vacuo* and recrystallization from benzene (1 g. per 2 ml.). The yield was 90%, m.p. 89–90°. Infrared absorption in Vb at λ_{max}^{Nujol} 6.12 and 10.18 μ (—C=C—) was absent in VIIIb.

Hydrocinnamoyl Chlorides.[25]—The *p*-fluoro compound (XIb) was obtained in 82% yield by heating VIIIb in benzene solution at reflux with a 40% excess of thionyl chloride for 90 min., then distilling the product, b.p. 54–58° (2 mm.).

The *m*,*p*-dichloro analog XIe, b.p. 96–100° (2 mm.), was best prepared (77% yield) from VIIIe in toluene solution at room temperature by adding a 10% excess of phosphorus pentachloride in portions, then stirring the solution at room temperature for 7 hr.

Anal. Calcd. for $C_9H_7Cl_3O$: C, 45.5; H, 2.97; Cl, 44.8. Found: C, 45.7; H, 3.15; Cl, 44.9.

Hydrocinnamic Esters.—The parent methyl ester IXa was obtained in 97% yield by hydrogenation of methyl cinnamate at 2 atm. with 5% palladium-carbon in benzene for 1 hr. The *p*-fluoro (IXb), *p*-chloro (IXc), *o*-chloro (IXd), and *m*,*p*-dichloro (IXe) esters were obtained in 80–90% yields by conventional esterification of the corresponding acids VIIIb,c,d,e with refluxing methanolic hydrogen chloride or with refluxing methanol containing acetyl chloride. Gas-liquid partition chromatography at 235°, using Dow Corning silicone oil supported on firebrick and helium as carrier gas, showed that IXc and IXd were of 100.0% and 99.7% purity, respectively. Alternatively, IXd of identical infrared spectrum and of 97.0% purity was prepared by hydrogenation at 1 atm. of methyl *o*-chlorocinnamate with intensively prereduced[10] palladium black in benzene for 3 hr. Satisfactory analytical data could not be obtained for these compounds.

2-Amino-4-hydroxy-6-phenethylpyrimidines (XIV).—Guanidine carbonate (4.70 g., 0.026 mole) was suspended in a solution of methyl 5-phenyl-3-ketovalerate (XIIIa) (11.5 g., 0.052 mole, calcd. as methyl ester) and 30 ml. of absolute ethanol. The mixture was refluxed for 18 hr. (guanidine carbonate gradually dissolves; the product gradually precipitates), then was diluted with 100 ml. of water and acidified to pH 5 with a few drops of acetic acid. Filtration of the chilled mixture afforded the solid product, which was washed with water and dried. See Table II for further data on XIVa, together with the data on XIVb and XIVe.

2-Amino-4-chloro-6-phenethylpyrimidines (XV).—A suspension of 0.014 mole of a 4-hydroxypyrimidine (XIV) in 12 ml. of phosphoryl chloride was heated at reflux for 45 min. The resulting solution was concentrated at reduced pressure, leaving a glassy residue which partly solidified on treatment with 50 ml. of ice water. This mixture was neutralized by dropwise addition of concd. ammonium hydroxide over a 3-hr. period, with stirring, until *p*H 8 was maintained. The solid product was separated from the supernatant in a centrifuge and dried to constant weight (*ca.* 95% yield). Material of purity sufficient for amination could be obtained by further washing with water and centrifugation until the supernatant was free of chloride ion. Generally it was more convenient to recrystallize the crude product directly by solution in 50 parts of warm dichloromethane, filtration, concentration of the filtrate to one-half volume, and addition of an equal volume of petroleum ether. Further data are in Table II.

2,4-Diamino-6-phenethylpyrimidines (II).—A suspension of 0.020 mole of a 4-chloro pyrimidine (XV) in 120 ml. of absolute ethanol which had been saturated at 0–5° with ammonia was sealed in a steel bomb (fitted with a stirrer) and heated at 140–150° (internal temperature) for 15 hr. The reaction mixture was concentrated *in vacuo* to a solid residue (wt. usually > 100% of theory), which was dissolved in 200 ml. of 50% aqueous acetic acid. Small amounts of solid were removed by filtration (any starting material would be recovered here) and the filtrate was made basic (*p*H 8–9) with 4 *M* sodium hydroxide and chilled to 5°. The precipitated product was collected on a filter and dried. Further data in Table II.

2,4-Diamino-6-phenethyl-*s*-triazines (III). Method A.—A stirred suspension of biguanide (X) (2.0 g., 0.020 mole) in 25 ml. of methanol was treated dropwise with 0.02 mole of a hydrocinnamic ester (IX), and the resulting mixture was stirred at room temperature for 20 hr. In the preparation

(17) Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Ultraviolet spectra were determined on a Model 11 Cary recording spectrophotometer. Infrared spectra (in Nujol mull or as the pure liquid) provided confirmatory evidence for the identity and purity of each compound described.

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of IIIb and IIIe, an initial heating to reflux for 1 or 2 min. was desirable. Compounds IIIb, IIIc, and IIIe formed a heavy precipitate within 3–4 hr., which prevented further stirring. Finally, the reaction mixture was chilled in ice and the product collected on a filter, washed with water, and dried; occasionally more material could be crystallized from the mother liquor. See Table III for further data.

Method B.—A solution of 2,4-diamino-6-*p*-fluorostyryltriazine (XVIIIb) (0.23 g., 1.0 mmole) in 25 ml. of 2-methoxyethanol was stirred with 0.10 g. of 5% palladium-on-carbon under hydrogen at 1 atm. for 35 min.; uptake ceased after 20 min. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated *in vacuo* to 8 ml. Dilution with water formed a white precipitate, which was collected on a filter, washed with water (two 5-ml. portions), and dried *in vacuo*. See Table III for further data (and results with XVIIIa→IIIa). Loss of ultraviolet absorption at 292 mμ characteristic of XVIIIb and infrared absorption at 10.19 μ (—C=C=C—) verified complete saturation of the double bond (XVIIIa lost bands at 297 mμ and 10.18 μ). Reduction of 2.5 g. of XVIIIb as a suspension in 2-methoxyethanol (200 ml.) formed a solution of the product, but pure IIIb could not be isolated from it.

2,4-Diamino-6-styryl-*s*-triazines (XVIII).—An intimate mixture of 0.04 mole of 2,4-diamino-6-methyltriazine (XVI) and 0.04 mole of a halobenzaldehyde (XVII) was suspended in 7.5 ml. of concd. sulfuric acid and heated on the steam bath. After 15 min., an additional 1.5 ml. of sulfuric acid was added, and the suspension was stirred briefly, then heated again for 45 min. The mixture was cooled to room temperature and 20 ml. of water was added cautiously, with ice cooling. The yellow product, a sulfate salt, was collected on a filter. This solid, pulverized and suspended in 20 ml. of water, was neutralized by treatment with saturated aqueous sodium bicarbonate while stirring until a *p*H of 7 was maintained. The free base was a white solid, removed by filtration and dried *in vacuo*. See further data in Table IV. Melting points are characteristically broad and somewhat variable and should not be used as sole criteria of purity.

Paper Chromatography.—All of the pyrimidines and triazines prepared (II, XIV, XV, III, XVIII) were, when purified, homogeneous by the descending paper chromatographic technique and, except for XIV, distinguishable from the immediate precursors in Schemes I and II. The following solvent systems were effective with Whatman No. 1 paper: A, 1-butanol–acetic acid–water (4:1:5); B, isopropyl alcohol–2 *M* hydrochloric acid (65:35); C, 2-methoxyethanol–water (9:1); D, benzene–methanol–water (2:6:1); E, water–saturated 1-butanol. Systems A, B, C, and E were used with pyrimidine derivatives, systems A, B, and D with the triazines. Spots were detected by visual examination under ultraviolet light.

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Potential Anticancer Agents.[1] LXXIII. Synthesis of Derivatives of 1-Deoxypsicose

ELMER J. REIST,[2a] PHILLIP A. HART, B. R. BAKER,[2b] AND LEON GOODMAN

Life Sciences Division, Stanford Research Institute, Menlo Park, Calif.

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The synthesis of 3,4,5,6-tetra-*O*-acetyl-1-deoxy-D-psicose (XII) via a condensation between 2,3,4,5-tetra-*O*-acetyl-D-ribonoyl chloride and dibenzyl malonate is described, together with its subsequent conversion to a series of ethyl β-thiopsicofuranosides. Certain analogies are made between derivatives of 1-deoxy-D-psicose and the corresponding derivatives of 2-deoxy-D-ribose.

A previous paper[3] from this laboratory described some model studies which were concerned with the synthesis of nucleosides derived from ketose sugars. It was demonstrated that D-fructose (IIa) could be readily transformed into either a furanose nucleoside (I) or pyranose nucleoside (III). The report by Schroeder and Hoeksema[4] of the successful synthesis of the antibiotic 9-β-D-psicofuranosyl adenine (VIa) (psicofuranine) from the blocked D-psicose (Va) suggests the generality of the nucleoside condensation with ketose sugars.

This convincing demonstration[3,4] of the ability of the ketose sugars to undergo nucleoside condensations, together with the report[4] that psicofuranine (VIa) showed marked antibacterial and antitumor activity, made it of interest to prepare some other ketose nucleosides as potential anticancer agents. The nucleoside chosen for study in the present work was 1′-deoxypsicofuranine (VIb).

The synthesis of a nucleoside such as VIb would be interesting from both the chemical and biological aspects. The presence of a methyl group vicinal to the potential reducing carbon of the sugar moiety may give a nucleoside such as VIb a chemical reactivity more closely related to that of the 2′-deoxynucleosides than to that of the ribonucleosides. If this should be true, this structural re-

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(2) (a) To whom inquiries should be sent; (b) School of Pharmacy, University of Buffalo.

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