chloro-5-phenylazopyridine[5] was autoclaved with an alcoholic solution of dimethylamine.

Experimental

Mills Reaction with 2-Dimethylamino-5-aminopyridine.—2-Dimethylamino-5-nitropyridine[6] was reduced in a Parr apparatus with 5% palladium on carbon in 95% ethanol. The diamine was unstable to air and on treatment with nitrosobenzene in acetic acid gave no isolable azo compound.

2-N,N-Dimethylamino-5-phenylazopyridine.—2-Chloro-5-phenylazopyridine, once recrystallized from ethanol, was prepared in 94% yield by the method of Mills.[5] Six grams of this compound was treated with a solution of 10.2 g. of dimethylamine in 65 ml. of absolute ethanol in a sealed tube at 150° for 4 hr. The solvent and excess dimethylamine were removed *in vacuo* and the product was recrystallized twice from ethanol; m.p. 114.5–115.2°; the yield of yellow plates was 3.4 g. (54.5%).

Anal. Calcd. for $C_{13}H_{14}N_4$: C, 69.03; H, 6.20; N, 24.77. Found: C, 68.95; H, 6.32; N, 24.55.

Biological Testing and Results.—Young male rats of the Sprague–Dawley strain, approximately 8 weeks of age and weighing 150 to 200 g., were distributed as equally as possible by initial body weight into groups of 10 animals each. Each group was fed a diet, patterned after the "low protein, low riboflavine" diet of Miller, *et al.*,[7] to which had been added one of the azo compounds at a level of 0.06%. The composition of the basal diet on a kilogram basis was as follows: crude casein, 120 g.; cerelose, 770 g.; Osborne and Mendel salt mixture, 40 g.; corn oil, 50 g.; Vitab (rice bran concentrate, obtained from Charles Bowman Co.), 20 g.; riboflavine, 0.5 mg.; vitamin A palmitate, 67,500 IU (we are grateful to Charles Pfizer and Co., Inc., for a generous supply). The control group received only the basal diet. All the rats were kept individually in screen-bottomed cages and were offered food and water *ad libitum*. Laparotomies were performed at the indicated times and microscopic examinations were made whenever an animal died or at the end of the experiment. Feeding 2-N,N-dimethylamino-5-phenylazopyridine at 0.06% level produced no tumors in 12 months. The data are indicated in Table I.

TABLE I

CARCINOGENICITIES OF THE AZO COMPOUNDS

Code	—Incidence of liver tumors[a]— 4 months	7 months	12 months
Control (no dye)	0/10	0/10	0/10
N,N-Dimethyl-*p*-phenylazoaniline[b]	7/10	9/10	10/10
N,N-Dimethyl-*p*-(3-pyridylazo)-aniline	1/8	7/8	8/8
5-Phenylazo-2-N,N-dimethylpyridine	0/10	0/10	0/10

[a] Number of rats with tumors/number of rats in experiment. All azo compounds were fed at the 0.06 level. [b] Commonly called Butter yellow.

(7) J. A. Miller and E. C. Miller, *Advan. Cancer Res.*, **1**, 339 (1953).

Some 5-Fluoropyrimidines[1a]

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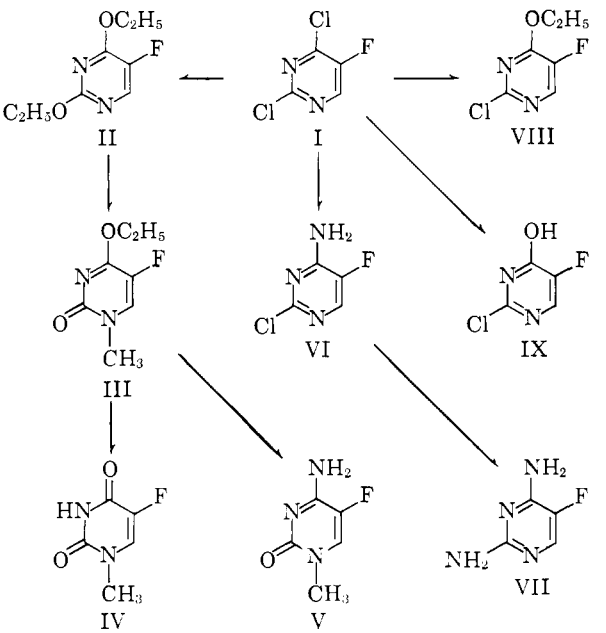
Since the synthesis of 5-fluorouracil by Duschinsky, Pleven, and Heidelberger[2] this compound has attacted a great deal of attention as an antimetabolite in the treatment of cancer.[3] Thus, it was desirable to prepare several derivatives of 5-fluoropyrimidine.

In this project the key intermediate was 2,4-dichloro-5-fluoropyrimidine (I).[4] The versatility of 2,4-dichloropyrimidines as intermediates in synthetic pyrimidine chemistry is well known[5] and is due to the reactive halogen atoms attached to the electrophilic pyrimidine ring. The conversion of I to 2,4-diethoxy-5-fluoropyrimidine (II) was effected with sodium ethoxide and is reported elsewhere.[6] Reaction of II with methyl iodide gave 4-ethoxy-5-fluoro-1-methyl-2(1H)-pyrimidone (III). The assignment of the methyl group to the N-1 position is based on the known reactions of 2,4-diethoxypyrimidines with alkyl halides and with O-acylglycosyl halides (Hilbert–Johnson synthesis of nucleosides) to yield N-1 alkyl derivatives and N-1 glycosyl nucleosides.[7] Hydrolysis and amminolysis of III resulted in the formation of 5-fluoro-1-methyluracil (IV) and 5-fluoro-1-methylcytosine (V), respectively.



Reaction of I with alcoholic sodium ethoxide (1 mole) or sodium hydroxide resulted in the formation of 2-chloro-4-ethoxy-5-fluoropyrimidine (VIII) and 2-chloro-5-fluoro-4-hydroxypyrimidine (IX), respectively.[8] Attempts to replace the chlorine atom of IX by amino or methoxy groups failed.

The partial structural relationship between the folic acid antagonist, aminopterin, and 2,4-diamino-5-

(1) (a) Supported largely by a Michigan Cancer Foundation Grant. (b) Chemistry Department, Le Moyne College, Syracuse, N. Y. 13214.

(2) R. Duschinsky, E. Pleven, and C. Heidelberger, *J. Am. Chem. Soc.*, **79**, 4559 (1957).

(3) J. A. Montgomery, *Cancer Res.*, **19**, 447 (1959).

(4) (a) R. Duschinsky, U. S. Patent 3,040,026 (1962); (b) M. G. Biressi, M. Carrissimi, and F. Ravenna, *Gazz. chim. ital.*, **93**, 1268 (1963); (c) L. D Protsenko and Yu. I. Bogodist, *Zh. Obshch. Khim.*, **33**, 537 (1963).

(5) D. J. Brown, "The Pyrimidines," Interscience Publishers, Inc., New York, N. Y., 1962, pp. 183–208.

(6) G. J. Durr, *J. Med. Chem.*, **8**, 140 (1965).

(7) G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 2001, 4489 (1930); J. J. Fox and I. Wempen, *Advan. Carbohydrate Chem.*, **14**, 328 (1959).

(8) Compound IX was prepared independently by Dr. R. Duschinsky of Hofmann-La Roche, Inc., who has verified that substitution took place at the 4-position. Dr. Duschinsky has also prepared and identified 2-chloro-5-fluoro-4-methoxypyrimidine. Allocation of the ethoxy group to the 4-position of VIII is based on analogy to this work: private communication by Dr. R. Duschinsky.

TABLE I

Compd.	Dose, mg./kg.	Survivors	Animal wt. diff. $T - C$[a]	Tumor wt., g. T/C[a]	% T/C[a]
		P1798 Lymphosarcoma			
II	250	0/10			
	62	10/10	−1.1	1810/2863	63
	62	10/10	0.2	1310/966	135
	62	6/10	−2.4	1233/1516	
		P1798 Lymphosarcoma			
III	250	0/10			
	50	10/10	−0.8	1410/2863	49
	50	10/10	−0.7	1337/1516	88
		HS1 Human Sarcoma (Embryonated Egg)			
VIII	20	6/6	−0.4	97/742	13
	20	3/6	0.0	358/890	
	20	2/6	−0.3	420/1308	
	10	3/6	−0.1	1100/1554	
	5	2/6	0.1	465/1116	
	2.5	5/6	0.0	335/682	49
	2.5	3/6	−0.3	388/1443	
		P1798 Lymphosarcoma			
IX	200	4/6	−4.5	122/1762	6
	200	2/6	−3.1	53/1706	
	200	0/6			
	100	1/6	−5.4	0/139	
	50	6/6	−5.1	105/1798	5
	50	6/6	−5.0	162/2170	7
	50	6/6	−3.6	182/1867	9
	50	5/6	−7.7	120/2293	5
		Sarcoma 180			
IX	50	6/6	−5.6	318/1753	18
	50	5/6	−1.6	484/2541	19
		Adenocarcinoma 755			
IX	50	10/10	−3.4	349/1480	23
	50	4/10	−7.5	180/1047	
	50	0/10			
	25	10/10	−4.1	392/1580	24

[a] T = test, C = control.

fluoropyrimidine (VII)[9] made the synthesis of VII particularly attractive. Attempts to prepare VII directly from I failed. Brown prepared 2,4-diaminopyrimidine by the reaction of 2,4-dichloropyrimidine with ammonia in phenol at 190°.[10] In order to avoid the use of boiling phenol, 2,4 diamino-5-fluoropyrimidine (VII) was finally prepared by reaction of 4-amino-2-chloro-5-fluoropyrimidine (VI) with alcoholic ammonia at 140° in a Parr bomb, the reaction being acid catalyzed by ammonium chloride. The 4-amino-2-chloro-5-fluoropyrimidine (VI) was prepared by a modification of the method described by Duschinsky.[4a]

Table I gives the screening test reports for these compounds. The testing was done under the auspices of the Cancer Chemotherapy National Service Center, and the testing procedures have been described previously.[11]

Compounds II–IV and VII–IX were without significant effect on L1210 lymphoid leukemia. The results of preliminary screening against P1798 lymphosarcoma were as follows: compounds V, VII, and VIII were nontoxic inactive; II and III passed stage 1 of sequential screen; IX passed second confirmation test of screen. Two compounds were screened against HS1 human sarcoma, II being nontoxic and inactive and VIII passing stage 2 of the screening. Of the three compounds tested against Sarcoma 180, IV and VI were without significant effect, and IX has passed stage 2 of the screening sequence. In testing against Adenocarcinoma 755, IV was without significant effect, IX passed stage 2 of the screening, and the other compounds have not been tested. The three compounds (VII–IX) tested against Dunning leukemia (ascites) were nontoxic and inactive. The parent compound, 5-fluorouracil (5FU),[2] showed significant inhibition against Sarcoma 180, L1210 leukemia, P1798 lymphosarcoma, and HS1 human sarcoma.[12] Insufficient data were obtained in testing 5FU against Adenocarcinoma 755.[13]

Experimental[14]

4-Ethoxy-5-fluoro-1-methyl-2(1H)-pyrimidone (III).—A solution of 700 mg. (3.7 mmoles) of II in 7 ml. of methyl iodide was allowed to stand for 2 days. The methyl iodide was removed *in vacuo*, and the residue was triturated with anhydrous ether and filtered, yielding 200 mg. of product, m.p. 129–133°. The ethereal filtrate was evaporated to an oil, and the above procedure was repeated twice (the methyl iodide solution now being refluxed) to yield an additional 300 mg. (m.p. 125–131°), giving a total yield of 77%. Recrystallization from 2-propanol–ether raised the m.p. to 135–136°; λ_{max}^{water} 282 mμ (log ε 3.90); λ_{max}^{Nujol} 6.01, 6.14, 6.55, 6.73, 7.48, 8.05, 8.59, 8.74, 9.09, 9.45, 9.80, 10.40, 10.71, 11.11, 12.98, 13.67, 14.54 μ.

Anal. Calcd. for $C_7H_9FN_2O_2$: C, 48.84; H, 5.27; F, 11.04. Found: C, 48.71; H, 5.25; F, 11.25.

5-Fluoro-1-methyluracil (IV).—A solution of 282 mg. (1.64 mmoles) of III and 10 ml. of 30% methanolic HCl was allowed to stand at room temperature for 3 days. During this time 170 mg. of product (m.p. 261–263°) crystallized and was removed by filtration. An additional 46 mg. (m.p. 257–259°) was obtained from the mother liquors increasing the yield to 92%. Recrystallization from 80% ethanol raised the m.p. to 264–265° when placed on the hot stage at 260°; λ_{max}^{water} pH 7: 274 mμ (log ε 3.84), pH 1.4: 273.5 mμ (log ε 3.84), pH 12.1: 271.5 mμ (log ε 3.70); λ_{max}^{Nujol} 5.95, 6.08, 7.59, 8.10, 8.31, 8.70, 9.32, 10.71, 11.10, 11.55, 12.80, 13.38, 14.31, 15.90 μ.

Anal. Calcd. for $C_5H_5FN_2O_2$: C, 41.67; H, 3.50; F, 13.19. Found: C, 41.95; H, 3.42; F, 13.48.

5-Fluoro-1-methylcytosine (V).—A solution of 142 mg. (0.83 mmole) of III and 10 ml. of 5% ethanolic ammonia was heated in a Parr bomb at 110° for 21 hr., the alcohol then being removed *in vacuo*. Addition of 1 ml. of water to the residue and filtration gave 45 mg. of product, m.p. 295–299°. An additional 38 mg. of product (m.p. 285–290°) was obtained from the filtrate raising the yield to 70%. Recrystallization was effected from 30% ethanol giving pure V: m.p. 297–299°; λ_{max}^{water} pH 7: 282 mμ (log ε 3.84), pH 1.3: 293.5 mμ (log ε 3.99), pH 12.2: 282 mμ (log ε 3.84); λ_{max}^{Nujol} 3.00, 3.18, 5.99, 6.20, 6.62, 7.00, 8.23, 8.78, 9.18, 9.48, 10.15, 12.85, 14.35 μ.

Anal. Calcd. for $C_5H_6FN_3O$: C, 41.97; H, 4.23; N, 29.37. Found: C, 42.10; H, 4.00; N, 29.31.

4-Amino-2-chloro-5-fluoropyrimidine (VI).—2,4-Dichloro-5-fluoropyrimidine (I, 200 mg., 1.2 mmoles) was added to 5 ml. of liquid ammonia in a pressure flask and allowed to warm to room temperature. The ammonia was then allowed to escape. On the

(9) The product VII was also prepared independently by Dr. R. Duschinsky.

(10) D. J. Brown, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **69**, 353 (1950).

(11) J. Leiter, A. R. Bourke, S. A. Schepartz, and I. Wodinsky, *Cancer Res.*, **20**, 734 (1960); J. Leiter, A. R. Bourke, D. B. Fitzgerald, S. A. Schepartz, and I. Wodinsky, *ibid.*, **22**, 221 (1962).

(12) Erich Hirschberg, *ibid.*, **23**, 606 (1963).

(13) D. P. Griswold, W. R. Lacter, Jr., M. Y. Snow, F. M. Schabel, Jr., and H. E. Shipper, *ibid.*, **23**, 343, 351 (1963).

(14) Melting points were determined using a Kofler hot stage. Paper chromatograms were carried out on Whatman No. 1 paper and the chromatograms were developed by a descending technique in the solvent systems (A) saturated aqueous ammonium sulfate–2-propanol–water (2:28:70) and (B) 2-propanol–water–concentrated HCl (6.5:77:16.5). After developing, the paper was dried and the spots were located by visual examination under ultraviolet light. Ultraviolet absorption spectra were determined on a Beckman DU spectrophotometer.

addition of water, 170 mg. (97%) of crude product, m.p. 192–194°, was obtained. Recrystallization from water gave needles, m.p. 194–195°. The pyrimidine VI traveled as a single spot on paper, R_f 0.67, solvent system A. Paper chromatography of the mother liquors showed the same spot only, thus indicating that the isomeric 2-amino-4-chloro-5-fluoropyrimidine was not formed in the reaction. The ultraviolet and infrared spectra were similar to those found by Duschinsky.[4a]

Anal. Calcd. for $C_4H_3ClFN_3$: C, 32.52; H, 2.05; Cl, 24.04; N, 28.49. Found: C, 32.46; H, 1.98; Cl, 24.28; N, 28.38.

2,4-Diamino-5-fluoropyrimidine (VII).—A mixture of 80 mg. (0.54 mmole) of VI, 5 ml. 5% ethanolic ammonia, and 200 mg. of ammonium chloride was heated at 140° for 19 hr. in a Parr bomb. The mixture was filtered, evaporated to dryness *in vacuo*, dissolved in 2 ml. of water, and brought to pH 12 with 0.2 ml. of 10% NaOH. This solution was evaporated to dryness *in vacuo*, and the desired product was separated by sublimation at 20 mm. and 140°, yielding 25 mg. (36%) of VII (m.p. 156–157° with partial recrystallization, remelting at 161–161.5°). Resublimation raised the m.p. to 164–165° with partial recrystallization, remelting at 166.5–167°; $\lambda_{max}^{pH\ 7\ buffer}$ 289 mμ (log ε 3.77); λ_{max}^{Nujol} 2.98, 3.15, 6.00, 6.23, 6.59, 6.71, 6.95, 8.25, 10.13, 10.65, 10.73, 12.90 μ.

Anal. Calcd. for $C_4H_5FN_4$: C, 37.51; H, 3.93; F, 14.83., Found: C, 37.65; H, 4.01; F, 15.11.

2-Chloro-4-ethoxy-5-fluoropyrimidine (VIII).—To a solution of 775 mg. (4.64 mmoles) of 2,4-dichloro-5-fluoropyrimidine (I) in absolute ethanol was added 2.9 ml. of 1.6 *N* ethanolic sodium ethoxide. The mixture was evaporated to 3 ml. and 7 ml. of water was added. An oil formed which solidified on cooling; this solid was removed by filtration, giving 800 mg. (96%) of product, m.p. 31–32°; purification by sublimation raised this to m.p. 35–36°; λ_{max}^{water} 261.5 mμ (log ε 3.72); λ_{max}^{film} 3.40, 6.35, 6.78, 6.90, 7.14, 7.45, 8.05, 8.21, 8.68, 9.80, 10.32, 10.50, 11.45, 12.45, 13.05 μ.

Anal. Calcd. for $C_6H_6ClFN_2O$: C, 40.80; H, 3.43; Cl, 20.05; F, 10.76. Found: C, 40.76; H, 3.40; Cl, 19.98; F, 10.52.

2-Chloro-5-fluoro-4-hydroxypyrimidine (IX).—A mixture of 1.96 g. (11.7 mmoles) of I and 6.2 ml. (11.8 mmoles) of 1.9 *N* NaOH was warmed to 45° and stirred for 45 min. at the end of which time the mixture was neutral. An additional 6.2 ml. of 1.9 *N* NaOH was added, and the mixture was stirred until the oil dissolved, requiring 15 min. After cooling, 1 ml. of concentrated HCl was added, causing the immediate precipitation of 1.38 g. of product, m.p. 170–171°. An additional 0.1 g. (same as above by infrared spectrum) was recovered from the filtrate giving a total yield of 85%. Evaporation of the mother liquors *in vacuo* gave a solid material whose infrared spectrum was similar to the pure product. Paper chromatography gave single identical spots for the pure compound and the residue in the mother liquor; solvent system A, R_f 0.76, for pure compound and residue; solvent system B, R_f 0.93, for pure compound and residue. Recrystallization from absolute ethanol, prolonged heating being avoided, raised the melting point to 176–177° with partial recrystallization and remelting at 228–243°; $\lambda_{max}^{0.1\ N\ CH_3OH}$ 229 mμ (log ε 3.72), 258–259 mμ (log ε 3.70); λ_{max}^{Nujol} 6.09, 6.28, 6.48, 6.65, 7.75, 8.00, 8.60, 10.39, 10.90, 12.78, 14.55 μ. The material is the same as that prepared and characterized by Duschinsky.[8]

Anal. Calcd. for $C_4H_2ClFN_2O$: C, 32.34; H, 1.36; F, 12.80. Found: C, 32.35; H, 1.42; F, 14.64.

Acknowledgment.—The author wishes to express his gratitude and thanks to Dr. R. Duschinsky of Hoffman-La Roche, Inc., Nutley, N. J.

New 1-Aminomethylbenzocyclobutenes

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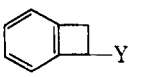
In view of the chemical uniqueness of a four-membered ring fused to an aromatic nucleus and the similarity of this system to the phenethyl chain, several amines containing the 1-benzocyclobutenyl group were synthesized for pharmacological evaluation. Until recently,[1] only two such compounds, 1-aminobenzocyclobutene[2] and N,N-dimethyl-1-aminomethyl-2-phenylbenzocyclobutene,[3] were known. In addition to the first amine, we have prepared four new 1-aminomethylbenzocyclobutenes and a related morpholine derivative.

1-Cyanobenzocyclobutene[4] (Ia), obtained by the benzyne-mediated cyclization of *o*-chlorohydrocinnamonitrile,[5] was hydrolyzed to benzocyclobutene-1-carboxylic acid (Ib). Treatment of the corresponding acid chloride Ic with sodium azide in toluene provided 1-aminobenzocyclobutene (Table I, III) in 40% yield. The direct conversion of the acid Ib to the amine III with hydrazoic acid[2] proceeded in somewhat higher yield.

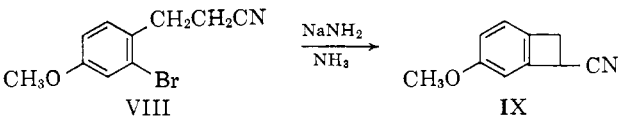


Ia, Y = CN IIa, Y = $CH_2NHCOCH_3$
b, Y = CO_2H b, Y = CH_2OTs
c, Y = COCl

1-Aminomethylbenzocyclobutene (IV) was prepared both by hydrolysis of the amide IIa from reductive acylation of 1-cyanobenzocyclobutene (Ia) and by lithium aluminum hydride reduction of the nitrile Ia.

The tosylate IIb of 1-hydroxymethylbenzocyclobutene was obtained with some modifications by the method of Cava and Mitchell[6]; aminolysis of this material with methylamine, dimethylamine, and morpholine provided compounds V, VI, and VII, respectively. As reported for the reaction of 1-hydroxymethyl-2-phenylbenzocyclobutene tosylate with dimethylamine,[3] the tosyl group of IIb is displaced without any apparent ring enlargement.[7] In order to substantiate the assigned structures, N,N-dimethyl-1-aminomethylbenzocyclobutene maleate (VI) was synthesized independently by reductive alkylation of 1-aminomethylbenzocyclobutene (IV) and was found to be identical by melting point and spectral comparison with the product obtained from the tosylate IIb.

Alkylation of ethyl cyanoacetate with 2-bromo-4-methoxybenzyl chloride, followed by hydrolysis of the resulting cyano ester and decarboxylation of the intermediate cyano acid, provided 2-bromo-4-methoxyhydrocinnamonitrile (VIII). Treatment of VIII with



VIII IX

sodamide in liquid ammonia afforded 1-cyano-5-methoxybenzocyclobutene (IX) in a 55% yield.

(1) After completion of this work, reports of amino- and aminoalkyl-substituted benzocyclobutenes appeared in the patent literature: (a) K. Ley, H. Walz, and W. Redetzky, Belgian Patent 630,171 (1963); (b) C. Kaiser and C. L. Zirkle, U. S. Patent 3,149,159 (1964); (c) Ciba S. A., French Patent 1,369,046 (1964).

(2) L. Horner, W. Kirmse, and K. Muth, *Chem. Ber.*, **91**, 430 (1958).

(3) A. T. Blomquist and C. G. Bottomley, *Ann.*, **653**, 67 (1962).

(4) M. P. Cava, R. L. Litle, and D. R. Napier, *J. Am. Chem. Soc.*, **80**, 2257 (1958).

(5) J. F. Bunnett and J. A. Skorcz, *J. Org. Chem.*, **27**, 3836 (1962).

(6) M. P. Cava and M. J. Mitchell, *ibid.*, **27**, 631 (1962).

(7) The quantitative conversion of 1-hydroxymethylindane tosylate to a 2-hydroxytetralin ester during formolysis has been noted by R. Huisgen G. Seidl, and I. Wimmer, *Tetrahedron*, **20**, 623 (1964).