additional 6.0 g. of green solid melting at 107–110°. The combined solids were recrystallized from ethyl acetate and 10 g. of a white solid which melted at 127–129° was obtained. After several recrystallizations from ethyl acetate the maleate (IIa) melted at 133–134° and exhibited a maximum at 290 mμ.

Anal. Calcd. for $C_{21}H_{23}O_4N_2Cl$: N, 6.95. Found: N, 6.65.

From the ethyl acetate filtrate there was obtained a second crop of 6.0 g. of a white solid which melted at 110–114°. After several recrystallizations from ethyl acetate, the maleate IIb melted at 123–124° and exhibited a maximum at 258 mμ. The melting point of a mixture of IIa and IIb was depressed (m.p. 111–113°).

Anal. Calcd. for $C_{21}H_{23}O_4N_2Cl$: N, 6.95. Found: N, 6.62.

The residual ethyl acetate filtrates were concentrated and the free base liberated from the oily maleate salt with a dilute sodium hydroxide solution. Upon fractional distillation there was obtained 4.5 g. of a yellow oil, b.p. 163–167° (1 mm.), $n^{26}D$ 1.5838, maximum at 256 mμ in ethanol.

1-(*p*-Chlorophenyl)-2-(2'-pyridyl)-4-N,N-dimethylamino-1-butene Oxalate.—A solution of 1.45 g. of II dissolved in a minimum of absolute ethanol was treated with an alcoholic solution of 0.45 g. of oxalic acid. Upon cooling 0.7 g. of a yellow solid separated which melted at 143–146°. After two recrystallizations from ethanol, the colorless solid melted at 159–160° and exhibited a maximum at 290 mμ in ethanol.

Anal. Calcd. for $C_{19}H_{21}O_4N_2Cl$: N, 7.43. Found: N, 7.49.

Ozonolysis of IIa.—A solution of 0.95 g. of the maleate IIa in 50 ml. of ethyl acetate was ozonized at −40° for three hours. The mixture was decomposed with dilute acetic acid and concentrated *in vacuo*. The brown residue was made basic with sodium carbonate solution, extracted with ether, the aqueous portion acidified with dilute hydrochloric acid and filtered. The crude solid when recrystallized from ethanol–water melted at 242–243° and did not depress the melting point of an authentic sample of *p*-chlorobenzoic acid (m.p. 241–242°).

Ozonolysis of IIb.—A solution of 4.0 g. of the free base (liberated from the maleate IIb, m.p. 120–123°), in 100 ml. of chloroform was ozonized at −40° for three hours. The mixture was decomposed with dilute acetic acid, the aqueous acidic layer separated and discarded. The chloroform layer was extracted with dilute sodium hydroxide solution, the basic layer separated, acidified with dilute hydrochloric acid and filtered. The crude solid, 0.72 g., after recrystallization from ethanol–water, melted at 239–240°, and did not depress the melting point of an authentic sample of *p*-chlorobenzoic acid.

Acknowledgment.—The authors wish to express their appreciation to Mr. Edwin Connor and his staff for the microanalyses and ultraviolet absorption spectra reported in this paper. We are grateful to Dr. William Tarpley[13] and Mr. Edward Townley for the solubility analysis studies.

(13) Aeroprojects, Inc., West Chester, Pennsylvania.

BLOOMFIELD, NEW JERSEY

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES, CO., INC., RAHWAY, NEW JERSEY]

Studies on Carcinolytic Compounds. VI. Substituted 2-(*Aldo*-Polyhydroxyalkyl)-benzimidazoles

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RECEIVED MARCH 20, 1956

A series of 2-(*aldo*-polyhydroxyalkyl)-benzimidazoles with chlorine or methyl substituents in the benzene ring has been prepared. Several of these compounds have been tested for activity against a lymphosarcoma in mice. The activity which was observed could be considered only a weak effect.

Several 2-(*aldo*-polyhydroxyalkyl)-benzimidazoles have been isolated as a result of side reactions in the use of imino ether hydrochlorides as ring closing agents in the formation of 1-glycosides of benzimidazoles from N-glycosides of 2-aminoanilines. Such a side reaction occurs under certain conditions during the synthesis of 1-α-D-ribofuranosyl-5,6-dimethylbenzimidazole (I), and 5,6-dimethyl-2-D-ribobenzimidazole (II) is also formed.[1] One of the 2-(*aldo*-polyhydroxyalkyl)-benzimidazoles was found to enhance the regression of a lymphosarcoma in mice. Consequently, a series of these compounds was synthesized and tested for carcinolytic activity.

Descriptions of compounds of this type have appeared in the literature in a number of publications including a review article.[2] Almost all of the benzimidazoles described in this paper have substituents in the benzene ring from among the following groups: 5-methyl, 5,6-dimethyl, 5-chloro and 5,6-dichloro. These 2-(*aldo*-polyhydroxyalkyl)-benzimidazoles are best prepared by the method of Moore and Link[3] and Dimler and Link[4] in which

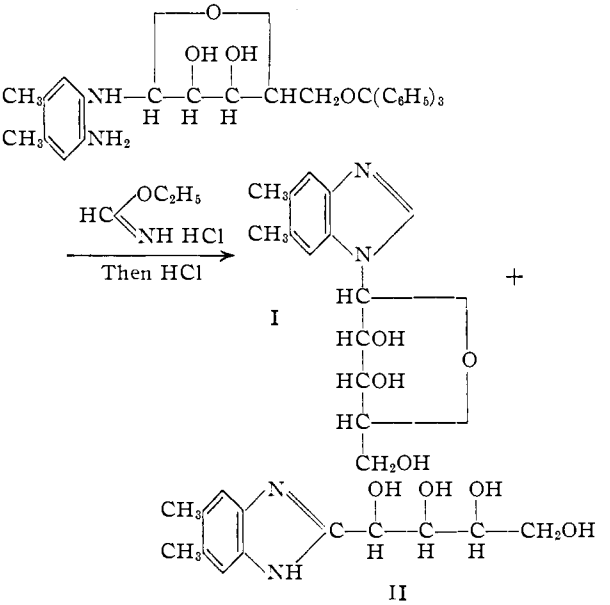

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TABLE I

PREPARATION AND PROPERTIES OF SUBSTITUTED 2-(*aldo*-POLYHYDROXYLALKYL)-BENZIMIDAZOLES

Product Substituted benzimidazole	Reactants: Potassium aldonate (g.)	Reactants: Substituted *o*-phenylenediamine (g.)	Yield, %	M.p., (dec.) °C.	$[\alpha]^{25}D \pm 2$ (*c* 2 in 5% citric acid)	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
5-Methyl-2-D-gluco[a]	14	7.7	80	205–206[b]	+10	$C_{13}H_{18}N_2O_5$	55.31	55.09	6.43	6.10	9.92	10.09
5-Methyl-2-D-ribo	16	10.8	77	192–193[c]	+17	$C_{12}H_{16}N_2O_4$	57.13	57.48	6.39	6.08	11.11	10.72
5-Methyl-2-L-arabo[d]	76	54	84	238–239[e]	+47	$C_{12}H_{16}N_2O_4$	57.13	57.10	6.39	6.20	11.11	11.01
5-Methyl-2-D-arabo	12.5	7.5	66	238–239[f]	−44[g]	$C_{12}H_{16}N_2O_4$	57.13	57.27	6.39	6.21	11.11	11.07
5-Methyl-2-D-galacto	11.7	6.1	60	222–223[e]	+42	$C_{13}H_{18}N_2O_5$	55.31	55.30	6.43	6.13	9.92	9.91
5-Methyl-2-D-manno	12[h]	6.1	49	228–229[b]	−20[g]	$C_{13}H_{18}N_2O_5$	55.31	55.17	6.43	6.19	9.92	9.60
5-Methyl-2-L-rhamno	18.3[i]	6.1	14	230–231[j]	+26[g]	$C_{13}H_{18}N_2O_4$	58.63	58.88	6.81	6.88	10.52	10.24
5,6-Dimethyl-2-D-ribo[k]	3.7	2.8	61	227–229[b]	+34[l]	$C_{13}H_{18}N_2O_4$	58.63	58.57	6.81	6.93	10.52	10.36
5,6-Dimethyl-2-L-arabo[m]	2.12	1.61	79	251–252[b]	+43[n]	$C_{13}H_{18}N_2O_4$	58.63	58.67	6.81	7.26	10.52	10.86
5-Chloro-2-D-gluco	14	8.5	60	227–229[e]	+ 9[o]	$C_{12}H_{15}N_2O_5Cl$	47.60	48.02	5.00	4.72	9.26	9.27
5-Chloro-2-D-ribo	13	9	41	235–236[e]	+20[p]	$C_{11}H_{13}N_2O_4Cl$	48.45	48.74	4.80	4.74	10.28	10.26
5-Chloro-2-L-arabo	12	8.5	46	241–242[e]	+45[o,q]	$C_{11}H_{13}N_2O_4Cl$	48.45	48.45	4.80	4.79	10.28	10.63
5-Chloro-2-D-galacto	14	9	38	240–242[e]	+40[p]	$C_{12}H_{15}N_2O_5Cl$	47.60	47.82	5.00	5.06	9.26	9.01
5-Chloro-2-D-manno	10[h]	9	38	235–236[b]	−19[g,n]	$C_{12}H_{15}N_2O_5Cl$	47.60	47.89	5.00	4.81	9.26	9.13
5-Chloro-2-L-rhamno	18.3[i]	9	34	234–235[j]	+25[g]	$C_{12}H_{15}N_2O_4Cl$	50.26	50.52	5.27	5.01	9.77	10.09
5,6-Dichloro-2-D-gluco	14	10	75	232–233[e]	+ 7[n,o,q]	$C_{12}H_{14}N_2O_5Cl_2$	42.75	42.76	4.18	4.17	8.31	8.64
5,6-Dichloro-2-D-ribo	13	10	57	239–241[e]	+16[o,q]	$C_{11}H_{12}N_2O_4Cl_2$	43.01	43.29	3.94	3.96	9.12	9.30
5,6-Dichloro-2-L-arabo	6.5	5	50	242–243[e]	+41[o,q]	$C_{11}H_{12}N_2O_4Cl_2$	43.01	43.29	3.94	3.64	9.12	9.12
5,6-Dichloro-2-D-galacto	14	10	38	262–263[e]	+43[o,q]	$C_{12}H_{14}N_2O_5Cl_2$	42.75	42.52	4.18	4.10	8.31	8.03
2-L-Lyxo	2[i]	0.7	28	192–192.5[j]	+14	$C_{11}H_{14}N_2O_4$	55.45	55.17	5.92	5.54	11.76	11.75

[a] D. A. Rosenfeld, J. W. Pratt, N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **73**, 5907 (1951). [b] Recrystallized from ethyl alcohol–water [c] The product, after being washed with ether, was redissolved in dilute hydrochloric acid, treated with Darco, and reprecipitated with ammonium hydroxide. It was then recrystallized three or four times from ethyl alcohol–water. [d] P. Griess and G. Harrow, *Ber.*, **20**, 3111 (1887). [e] The product was purified by dissolution in dilute hydrochloric acid followed by reprecipitation with ammonium hydroxide. This operation was repeated three or four times. [f] The product was dissolved in dilute hydrochloric acid and reprecipitated with ammonium hydroxide. It was then recrystallized once from ethyl alcohol–water. [g] *T*, 21°. [h] A hygroscopic sirup. [i] Barium salt. [j] Recrystallized from water. [k] Picrate made: m.p. 206.5–207° dec.; $[\alpha]^{24}D + 33 \pm 2$ (*c* 1 in pyridine). *Anal.* Calcd. for $C_{19}H_{21}N_5O_{11}$: C, 46.06; H, 4.27; N, 14.14. Found: C, 46.24; H, 4.21; N, 13.98. [l] *c* 1 in pyridine; *T*, 24°. [m] Picrate made: m.p. 215–216°. *Anal.* Calcd. for $C_{19}H_{21}N_5O_{11}$: C, 46.06; H, 4.27; N, 14.14. Found: C, 46.26; H, 4.55; N, 14.22. [n] *c* 1. [o] *T*, 26°. [p] *T*, 24°. [q] Rotation determined in 0.3 *N* hydrochloric acid.

the sugars are converted to the potassium salts of the aldonic acids, and the latter are condensed with the appropriate *o*-phenylenediamines under acid conditions to form the benzimidazoles.

Preliminary tests[5,6] on several of these compounds for activity against tumors in mice were carried out in these laboratories. For instance, 5-methyl-2-L-arabobenzimidazole was tested for its effect in enhancing the regression of lymphosarcoma (6C3H-ED) transplants in mice of the C3H strain. Adult mice maintained on a stock ration were inoculated with about 10,000 cells. The animals were transferred to a riboflavin deficient diet at 13 days post transplant. One group of mice was untreated (other than for the feeding of the riboflavin-deficient diet) and served as controls. The experimental group received 1 mg. of 5-methyl-2-L-arabobenzimidazole (in gum acacia) *per os* daily. This compound was tested in three successive groups of mice, with controls. In one group of animals there was an indication that the compound was effective in enhancing a regression of the well established tumor transplants. Other compounds which were tested, but which showed no activity in a single test, were 5-methyl-2-D-glucobenzimidazole, 5-methyl-2-D-ribobenzimidazole, 5,6-dimethyl-2-D-ribobenzimidazole, 5,6-dimethyl-2-L-arabobenzimidazole, 5,6-dichloro-2-L-arabobenzimidazole and 2-D-ribobenzimidazole.

The possible activity indicated by the one group of mice after administration of 5-methyl-2-L-arabobenzimidazole was of sufficient interest that we were led to submit the compounds for further study to Dr. C. Chester Stock of the Sloan-Kettering Institute for Cancer Research. Some of these compounds were found to show some activity in inhibiting tumor growth; a detailed report of this work will be published elsewhere by Dr. George Tarnowski and Dr. Chester Stock.

Experimental[7]

Both the oxidations of the sugars with potassium hypoiodite and the condensations of the aldonic acids with the *o*-phenylenediamines were carried out according to published procedures.[3,4] The diamines were either available commercially or obtained by reduction of the corresponding nitro compounds.[8,9] Details concerning the purification and properties of the individual benzimidazoles are included in Table I.

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(7) We are indebted to Mr. Richard Boos and his associates for the microanalyses.

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