was filtered, washed well with water, and dried; wt. 2.2 g., m.p. 284–295° dec. A solution of 1.5 g. of this carboxylic acid in 25 ml. of redistilled quinoline was refluxed for 1 hr., cooled, and poured into ice–dilute hydrochloric acid. The precipitate was collected by filtration, washed well with water, and dried; wt., 1.15 g., m.p. 289–292°. Recrystallization from glacial acetic acid gave pure product, m.p. 292–293°.

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 69.0; H, 5.8; N, 16.1. Found: C, 68.7; H, 6.1; N, 16.2.

Biological Activity Against Spontaneous Mammary Cancers.—The ability of some of the foregoing compounds to cause regression and cure of spontaneous mammary cancers of SPFS mice has already been described.[1] The most active found was a mixture of 1,2-dichloro-4-benzenesulfonamido-5-nitrobenzene and 1,2-dimethyl-4-*p*-carboxyphenylazo-5-hydroxybenzene.[5] Similar assay of most of the other compounds in the series has shown that they were either less active or were without activity against these spontaneous cancers.

Substituted 2-Aminobenzimidazoles[1]

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Received May 6, 1963

As part of our continuing studies on the physical and physiological properties of benzimidazole derivatives[2] we wish to report at this time a number of hitherto undescribed 2-aminobenzimidazoles and a preliminary report of their physiological activity. Although several methods for the synthesis of 2-aminobenzimidazoles have been reported,[3] remarkably few of these have been described.[4] This is somewhat surprising in view of the simplicity of synthesis and the fact that this type of compound is of chemical interest considered as disubstituted guanidines.

After screening for circulatory effects of the compounds the most marked effect was observed on the conductive mechanism of the heart. Administered intravenously to cats and rabbits it was found that 2-aminobenzimidazole and the methyl-substituted derivatives caused a defect in the normal conductive processes of the heart as indicated by a 50–100% increase in the QRS interval and a 30–50% increase in the PR interval of the electrocardiogram.[5] 2-Amino-5-chlorobenzimidazole and 2-amino-1-phenylbenzimidazole were ineffective under the same experimental conditions. Increased activity was noted among the effective compounds with increased substitution of methyl groups in the benzene ring. A methyl group in the 1-position generally decreased effectiveness.

Experimental

For the synthesis of the present compounds we have utilized the procedure in which an appropriate *o*-phenylenediamine is condensed with cyanogen bromide.[3b] We have found (in distinction to the previous workers) that the reaction mixture can be worked up after 15 min. and that ammonium hydroxide may be used instead of sodium hydroxide to isolate the product from the acidic reaction mixture. Otherwise the procedure is the same as the one previously reported. The compounds prepared in this work are shown in Table I. The first five compounds listed were synthesized from *o*-phenylenediamines obtained commercially. The others were synthesized from known N-methyl-*o*-phenylenediamines prepared from appropriate *o*-nitroaniline by the series of reactions: tosylation,[6] methylation,[6] detosylation,[6] and reduction.[7]

Biological Testing.—Male and female cats and rabbits weighing 2–3 kg. were anesthetized lightly with sodium pentothal. The right common carotid artery and the external jugular vein were isolated and the two vessels cannulated proximally and tied off. The cannula in the jugular vein was attached to a Phipps-Bird constant injection apparatus and the cannula in the carotid artery was connected to a Sanborn pressure transducer. Electrodes were placed on the animal's legs and the electrocardiogram and blood pressure recorded on a Sanborn Twin-Viso recorder. The compounds were tested by dissolving them in distilled water with the aid of hydrochloric acid (pH of the final solution, 5–6). The animals served as their own controls. When the blood pressure became stabilized and the animal registered a normal electrocardiogram the test compound was administered at a rate of 5 mg./min./kg. in 0.2 ml. of solution.

TABLE I

SUBSTITUTED 2-AMINOBENZIMIDAZOLES

2-Aminobenzimidazole	Average yield, %	M.p.,[a] °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found[b]
5-(or 6-)CH_3	65	203–204[c]	$C_8H_9N_3$	65.31	65.20	6.12	6.12
5,6-$(CH_3)_2$	60	228–229	$C_9H_{11}N_3$	67.08	67.37	6.83	6.83
4,6-(or 5,7)-$(CH_3)_2$	55	215–216	$C_9H_{11}N_3$	67.08	67.22	6.83	6.79
5-(or 6)-Cl	60	169–170[d]					
1-C_6H_5	60	154–155	$C_{13}H_{11}N_3$	74.64	74.36	5.26	5.35
1-CH_3	75	202–203[e]	$C_8H_9N_3$	65.31	65.58	6.12	6.47
1,5-$(CH_3)_2$	57	235–236	$C_9H_{11}N_3$	67.08	66.83	6.83	6.80
1,5,6-$(CH_3)_3$	83	259–260	$C_{10}H_{13}N_3$	68.57	68.80	7.43	7.66

[a] Fisher–Johns hot stage. [b] Analyses by C. F. Geiger, Ontario, Calif. [c] Lit.[3e] m.p. 196–197. [d] Lit.[3b] m.p. 167–168°. [e] Lit.[3e] m.p. 200–201.

Acknowledgment.—The author is indebted to Lawrence A. Babbitt, Alfred LeBouton, Charles Sheehan, and Alfred C. Rice for assistance in the biological testing.

(1) This investigation was supported by the San Diego County Heart Association and in part by Public Health Service Research Grant HS 6792.

(2) L. Joseph and J. Julca, *J. Org. Chem.*, **27**, 1101 (1962).

(3) (a) P. Pierron, *Ann. Chim.*, [8] **15**, 191 (1908); (b) N. J. Leonard, D. Y. Curtin, and K. M. Beck, *J. Am. Chem. Soc.*, **69**, 2459 (1947); (c) L. S. Efros, B. A. Porai-Koshits, and S. G. Farbenstein, *J. Gen. Chem. USSR*, **23**, 1961 (1953); (d) N. D. Vitkevich and A. M. Simonov, *ibid.*, **29**, 2578 (1959); (e) N. P. Bednyagina and I. Ya. Postovskii, *ibid.*, **30**, 1456 (1960).

(4) A considerable number of benzimidazole carbamic acids and their esters have been reported in the patent literature, *e.g.*, H. L. Klopping, U. S. Patent 2,933,504 (1960), and H. M. Loux, U. S. Patent 3,010,968 (1961). These compounds may be looked upon as 2-aminobenzimidazoles which have been substituted on the amino group. The present compounds contain an intact amino group.

(5) G. E. Burch and T. Winsor, "A Primer of Electrocardiography," 4th Ed., Lea and Febiger, Philadelphia, Pa., 1960, p. 86.

(6) E. H. Usherwood and M. A. Whitely, *J. Chem. Soc.*, 1084 (1923).

(7) D. Balcom and A. Furst, *J. Am. Chem. Soc.*, **75**, 5334 (1953).