infrared spectrum indicates a carboxyl group and possible amide carbonyl.

The antibiotic gives negative Tollens, 2,4-dinitrophenylhydrazine, and ninhydrin tests. In glacial acetic acid or carbon tetrachloride, bromine is rapidly absorbed with evolution of hydrogen bromide. The color of permanganate is quickly discharged by the antibiotic in aqueous solution. On heating a strongly alkaline solution in the presence of lead acetate a slight darkening results and ammonia is evolved. A white precipitate results with mercuric chloride, but no reaction with mercuric oxide.

Aqueous solutions of the antibiotic are quite stable over a wide *p*H range at room temperature. The crystalline antibiotic can be stored for long periods of time with no loss in potency.

This antibiotic exhibits a very low order of toxicity, but preliminary animal protection studies indicate that the new antibiotic is not active *in vivo*.

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RECEIVED MAY 16, 1952

ACIDIC BEHAVIOR EXHIBITED BY METHYL BORATE TOWARD AMINES[1]

Sir:

The question of the ability of alkyl borates to form addition compounds with amines under ordinary conditions has not as yet been settled. Such compounds have not been reported, and it has been suggested[2] that they do not form.

We have found, however, that the lowest boric ester (and presumably the least hindered), methyl borate, forms white solid addition compounds when treated with a number of amines, including dimethylamine, diethylamine, di-*n*-propylamine, di-*n*-butylamine, di-*n*-amylamine, triethylamine, tributylamine, ethylenediamine, piperidine, methylamine, and *t*-butylamine. In the case of the last four amines, the compounds are stable enough to be purified by sublimation *in vacuo*, weighed, and analyzed. No evidence of interaction has been obtained in the case of the weaker bases pyridine and quinoline.

These addition reactions are strongly catalyzed by the lower aliphatic alcohols, the degree of catalysis increasing with the acidity of the alcohol.

The addition compounds thus far characterized are listed in the accompanying table.

Compound	M.p., °C.	Analyses, % Calcd.	Found
$(CH_3O)_3B{:}NH_2CH_2CH_2NH_2$	81–82	B, 6.71	6.72
$(CH_3O)_3B{:}H{-}N\langle\bigcirc\rangle$	75	B, 5.82	5.77
$(CH_3O)_3B{:}NH_2CH_3$	67	N, 10.37	10.44
$(CH_3O)_3B{:}NH_2C(CH_3)_3$	67–70	B, 6.01	6.22

Solid compounds do not seem to separate when the amines and ethyl borate are mixed under the same conditions. However, there is considerable heat evolved during mixing, indicating some chemical interaction between components. When amines are added to the higher esters, *n*-butyl- and *n*-amyl borates, there is no appreciable heat effect. It seems likely, therefore, that the stabilities of such amine-borate complexes are governed largely by steric factors.

We are at present unable to propose a reasonable mechanism explaining the catalysis of these addition reactions by alcohols. Studies on the heats of formation of these complexes are being carried out.

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(1) Based on research carried out under Signal Corps Contract DA 36-039 Sc-5492 between the Squier Signal Laboratory and the Polytechnic Institute of Brooklyn.

(2) N. V. Sidgwick, "Chemical Elements and Their Compounds," Oxford University Press, London, 1950, p. 403.

SOME ANTIMETABOLITES OF SEROTONIN AND THEIR POSSIBLE APPLICATION TO THE TREATMENT OF HYPERTENSION

Sir:

The recent elucidation of the structure of serotonin, the vasoconstrictor of serum,[1-3] has provided an opportunity for the testing of a basic postulate in the chemotherapy of non-infectious diseases. This postulate is that if such diseases arise from excess of specific hormones or other metabolities, they may be susceptible to treatment by antimetabolities, which would thus nullify these extra amounts.[4] Experimental models to test this idea have been described for thyroxine, and for other metabolities.[5,6] The use of some of the antihistamines in medicine is an unconscious application of the same principle.[6] If serotonin, which is the naturally occurring vasoconstrictor in mammals were to be increased in an animal, either by excessive synthesis or decreased destruction, it would not be difficult to envision it as the cause of certain clinical hypertensions. We have therefore attempted to produce antimetabolities of serotonin, in the hope that they may be useful pharmacological agents.

Several new 5-aminoindoles with alkyl groups in positions 2 and 3 have been made by reduction of the corresponding 5-nitroindoles prepared by the Fischer synthesis.[7,8] The structural resemblance to serotonin, 3-aminoethyl-5-hydroxyindole, is clear. These were tested on ring-shaped segments of sheep carotid artery for ability to prevent the constriction which serotonin causes. A roughly quantitative test was developed to allow comparison of various analogs, and to permit study of the competitive nature of the antagonism.

The most active antimetabolite examined was 2-methyl-3-ethyl-5-aminoindole, m.p. 148–149° (calcd. C, 75.84; H, 8.10; N, 16.08; found, C, 75.77; H, 7.83; N, 16.33). A maximal contraction

(1) M. Rapport, *J. Biol. Chem.*, **180**, 961 (1949).
(2) K. E. Hamlin and F. E. Fischer, THIS JOURNAL, **73**, 5007 (1951).
(3) M. E. Speeter, R. V. Heinzelman and D. I. Weisblat, *ibid.*, **73**, 5515 (1951).
(4) D. W. Woolley, *Science*, **100**, 579 (1944).
(5) D. W. Woolley, *J. Biol. Chem.*, **164**, 11 (1946).
(6) D. W. Woolley, "A Study of Antimetabolities," John Wiley & Sons, New York, N. Y., 1952.
(7) H. Bauer and E. Strauss, *Ber.*, **65**, 308 (1932).
(8) K. Schofield and R. S. Theobald, *J. Chem. Soc.*, 1505 (1950).

(1/3 decrease in diameter) of the artery rings was produced by 0.2 γ of serotonin[9] per cc. When 20 γ of this analog was then applied, the effect of serotonin was completely abolished. Half maximal antagonism was observed with 5–10 γ. The corresponding 2,3-dimethyl analog[7] was slightly less active, and the corresponding 3-ethyl analog, m.p. 116–118° (calcd. C, 74.97; H, 7.55; found, C, 74.94; H, 7.57) was somewhat less than the dimethyl. The analogs by themselves did not cause relaxation of segments untreated with serotonin. The antagonism between serotonin and analog was competitive over a serotonin concentration of 0.1–2.0 γ per cc. Some antagonism could also be shown in intact guinea pigs. The toxicity of the 2,3-dimethyl-5-aminoindole for either mice or guinea pigs was low enough (150 mg. per kg. for first signs of distress) as to suggest that such antimetabolities of serotonin may be useful pharmacological agents. Further application of established principles[6] may result in even more potent compounds.

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(9) Serotonin was kindly supplied by the Abbott Laboratories.
(10) With the technical assistance of G. Schaffner.

THE DETECTION, ISOLATION AND IDENTIFICATION OF (−)-PIPECOLIC ACID AS A CONSTITUENT OF PLANTS

Sir:

By partition chromatography on paper an unidentified ninhydrin reacting constituent of the alcohol soluble (non-protein) nitrogen fraction of beans was detected and found to be present in the fresh fruit and dry seeds of legumes.[1] The R_F values in phenol, collidine–lutidine and butanol-acetic acid were 0.90, 0.38, and 0.21, respectively. This substance has now been isolated by the use of an ion exchange resin (Zeo-Rex). 800 mg. of pure (−)-pipecolic acid hydrochloride (piperidine-2-carboxylic acid) was isolated from approximately 10 kg. of fresh green beans (*Phaseolus vulgaris*).

A blue reaction with isatin on the chromatograms first suggested that the substance was a piperidine or pyrrolidine derivative. When the substance was finally isolated it proved to be indistinguishable in phenol, collidine–lutidine, and butanol–acetic acid chromatograms from synthetic (DL)-pipecolic acid prepared by catalytic reduction of α-picolinic acid. The two isomeric piperidine carboxylic acids were distinguishable chromatographically from the isolate in the solvents collidine-lutidine and butanol–acetic acid.

Infrared absorption spectra, obtained for us by Dr. H. Posvic,[2] of the isolated crystalline substance and of the (DL) synthetic product were similar but not identical and the X-ray diffraction patterns of the two compounds were dissimilar. The synthetic product apparently crystallized as a racemic compound; and only when the natural product was compared with the optically active (−)-enantimorph[2] did it prove to be identical as shown by matching infrared absorption spectra. The free acid and its hydrochloride are very soluble in water, sparingly so in ethanol, insoluble in benzene and petroleum ether and they are particularly insoluble in the solvents suitable for infrared absorption spectroscopy. The optically active (−) enantimorph as the free base was obtained from King[3] who prepared it by reduction of baikiain ((−)1,2,3,6-tetrahydropyridine-2-carboxylic acid), a substance isolated from a leguminous wood (Rhodesian teak). For purposes of infrared comparison with the isolate the hydrochloride was prepared in crystalline form from King's reduction product.

This evidence together with an ultimate analysis of the isolate, proves that the naturally occurring substance is (−)-pipecolic acid. (Found: C, 43.40; H, 7.30; N, 8.54; calcd. for $C_6H_{11}O_2NHCl$: C, 43.51; H, 7.30; N, 8.46). The isolate melted at 257–258° with decomposition and its rotation $[\alpha]^{23}D$ was −10.3°.

Pipecolic acid is a prominent constituent of leguminous fruits and seeds and appears also to be present in a large number of other plants (*e.g.*, potato tuber, the edible mushroom) though in smaller amount. Further details will be published later.

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(1) Unknown No. 1 in Figure 2 of F. C. Steward and J. F. Thompson, *Ann. Rev. Plant Physiology*, **1**, 233–264 (1950).
(2) Chemistry Department, Cornell University, Ithaca, N. Y.
(3) F. E. King, T. J. King and A. J. Warwick, *J. Chem. Soc.*, 3590–3597 (1950).