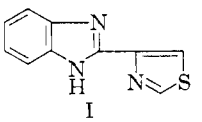
suggests a unique interference with a metabolic pathway essential to a variety of helminths.

2-(4′-Thiazolyl)-benzimidazole (I, generic name: thiabendazole) was outstanding in anthelmintic activity among several hundred analogs studied in some detail. Reaction of 4-thiazolecarboxamide[2] with *o*-phenylenediamine in polyphosphoric acid[3] at 250° for three hours gave a 64% yield of I which melted at 304–305°, $\lambda_{max}^{CH_3OH}$ 298 mμ ε 23,330.[4]



I

Compounds with substituents at positions C_1, C_2 and C_5 of the benzimidazole ring were synthesized and examined for anthelmintic activity. Treatment of the anion (sodium hydride in benzene–dimethylformamide) of I with methyl iodide gave the 1-methyl derivative of I, m.p. 139–140°, similarly 1-benzoyl I, m.p. 147°. 4-Methyl-2-nitroaniline was acylated with 4-thiazolylcarboxylic acid chloride, and the resulting nitroanilide was reduced catalytically (Pd–C). Cyclization of this *o*-aminoanilide with hydrochloric acid in refluxing alcohol gave 5-(or 6)-methyl I, m.p. 234–235°. 5-Carbomethoxythiazole[5] was heated with *o*-phenylenediamine in polyphosphoric acid to 175° to give 2-(5′-thiazolyl)-benzimidazole, m.p. 294–295°, $\lambda_{max}^{CH_3OH}$ 311 mμ ε 20,280. 2-Naphthaldehyde, *o*-phenylenediamine and copper acetate[6] reacted to give 2-(2′-naphthyl)-benzimidazole, m.p. 215–216°. $\lambda_{max}^{CH_3OH}$ 317 mμ ε 30,060.

If the anthelmintic potency of I for gastrointestinal parasites in sheep is regarded as 1.0, selected compounds have these approximate potencies: 2-(2′-furyl)-[6,7] (0.60); 2-phenyl-[3] (0.25); 2-(2′-naphthyl)-(0.1); 2-(5′-thiazolyl)-(isomer of I) (0.1); 5-(or 6)-methyl I (0.5). Phenothiazine on a similar scale is 0.05 or less.

Thiabendazole has significant anthelmintic activity for gastrointestinal parasites in sheep, goats, cattle, horses, swine, dogs and poultry. This compound is well-tolerated and does not stain the skin, hair or wool of animals. It may be given orally for therapeutic use or in feed or mineral supplements for the prophylactic control of parasites in domestic animals. In sheep, for example, thiabendazole in a single oral dose of 50 mg./kg. of body weight removed more than 95% of the worms belonging to ten genera of gastrointestinal parasites (*Trichostronogylus, Cooperia, Nematodirus, Ostertagia, Haemonchus, Oesophagostomum, Bunostomum, Strongyloides, Chabertia, Trichuris*). In addition to removing the adult parasites, thiabendazole inhibits production of eggs and interferes with development of larval forms. An effect has been observed on the migrating parasitic stages of roundworm and kidney worm in swine. Since thiabendazole has anthelmintic activity for hookworm, roundworm (*Ascaris*), and whipworm infections in dogs, its effect on similar parasites in man is under investigation.

Acknowledgment.—The authors are indebted to Dr. A. Zeissig for stimulating the search for agents effective against helminths of ruminants, to Dr. J. Tiner for preliminary phases of assay methodology and to Drs. C. Shunk and K. Folkers for a sample of 2-phenylbenzimidazole which was one of the early compounds showing broad spectrum activity in sheep.

H. D. BROWN
A. R. MATZUK
MERCK, SHARP & DOHME I. R. ILVES
RESEARCH LABORATORIES L. H. PETERSON
S. A. HARRIS
L. H. SARETT
MERCK INSTITUTE J. R. EGERTON
FOR THERAPEUTIC J. J. YAKSTIS
RESEARCH W. C. CAMPBELL
RAHWAY, N. J. A. C. CUCKLER

RECEIVED FEBRUARY 22, 1961

(2) H. Erlenmeyer and C. J. Morel, *Helv. Chim. Acta*, **28**, 362 (1945).

(3) *Cf.* D. W. Hein, R. J. Alheim and J. I. Leavitt, *J. Am. Chem. Soc.*, **79**, 427 (1957).

(4) This and subsequent products described gave satisfactory elemental analyses.

(5) H. Erlenmeyer, W. Mengisen and B. Prijs, *Helv. Chim. Acta*, **30**, 1865 (1947).

(6) Rudolf Weidenhagen, *Ber.*, **69**, 2263 (1936).

(7) 2-(2-Furyl)-benzimidazole is more than four times as toxic as thiabendazole and analogs cited above when administered as a single oral drench dose to sheep.

THE PLANT SULFOLIPID. IDENTIFICATION OF 6-SULFO-QUINOVOSE[1]

Sir:

The sulfolipid occurring in all photosynthetic tissues investigated was presumed to be a sulfoglycosyl glyceride[2] on the basis of radiochromatographic evidence. Deacylation of the lipid yielded a glycoside which was isolated by ion exchange resin chromatography.[3] The glyceryl sulfoglycoside exhibited a molecular rotation, $[M]^{25}D$ of + 31,000°, characteristic of alkyl α-D-glucopyranosides. The α-glycosidic configuration was further indicated by observation of a nuclear magnetic resonance absorption characteristic of an equatorial anomeric proton.[4] The rotational shift in cupra $B^{3,5}$ of −370° indicated three adjacent equatorial hydroxyl groups as in glucosides. The glyceryl sulfoglycoside was converted to a methyl sulfoglycoside whose properties were compared with those of methyl 6-sulfo-6-deoxy-α-D-glucopyranoside (methyl 6-sulfo-α-D-quinovoside). This was prepared from the sulfosugar obtained by bisulfite displacement of 6-tosyl-1,2-isopropylidene-D-glucose. The melting point of the cyclohexylammonium methyl sulfoglycosides, 173–174°, was unaltered by admixture. Infrared absorption spectra of the two were identical and differed markedly from that of cyclohexylammonium methyl glucoside-6-sulfate. The natural and synthetic sulfodeoxyglucoses exhibited identical R_f values upon paper chromatography and were separable from synthetic 6-sulfo-6-deoxy-D-galactose-S^{35}.

(1) This work was supported by the National Science Foundation, the Atomic Energy Commission, the National Institute of Arthritis and Metabolic Diseases of the Public Health Service and the Pennsylvania Agricultural Experimental Station.

(2) A. A. Benson, H. Daniel and R. Wiser, *Proc. Nat. Acad. Sci.*, **45**, 1582 (1959).

(3) M. Lepage, H. Daniel and A. A. Benson, *J. Am. Chem. Soc.*, **83**, 157 (1961).

(4) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein and W. G. Schneider, *ibid.*, **80**, 6098 (1958).

(5) R. E. Reeves, *ibid.*, **72**, 1499 (1950).

The occurrence of the sulfonic acid group in a hexose molecule suggests function of sulfocarbohydrate metabolism in Nature. The sulfolipid[6] itself is unique among known lipids in possessing a readily metabolizable but chemically stable sulfonate radical which gives the lipid its strongly surfactant properties.

(6) The term sulfolipid denotes the sulfonic acid group. Those lipids such as cerebroside sulfuric ester have similar physical properties but must be classified as sulfatides because of their sulfate ester structure. Other neutral sulfur-containing lipids such as those in yeast and in lesser quantities in plants may be classified as thiolipids.

(7) Organisch Chemisches Institut der Technischen Hochschule, Munich.

H. DANIEL[7]
M. MIYANO
R. O. MUMMA
T. YAGI
M. LEPAGE
I. SHIBUYA
A. A. BENSON

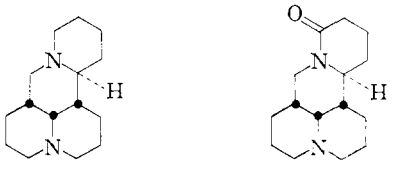
DEPARTMENT OF AGRICULTURAL AND BIOLOGICAL CHEMISTRY
THE PENNSYLVANIA STATE UNIVERSITY
UNIVERSITY PARK, PENNSYLVANIA

RECEIVED FEBRUARY 17, 1961

THE SYNTHESIS OF *dl*-MATRIDINE

Sir:

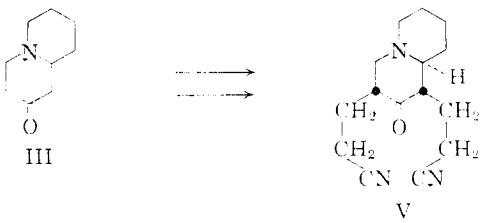
We wish to report the synthesis of *dl*-matridine, I, a reduction product of matrine,[1] II, the principal alkaloid of *Sophora flavescens* Ait.[2] The relative stereochemistry as represented in I and II has been established by several groups of workers[1,2,3,4]



I II

and is confirmed by the synthetic route herein reported. This route is an extension of the method we reported earlier[5] for the synthesis of hexahydrojulolidine which utilizes as an important step the bis alkylation of enamines with acrylonitrile after the method of Stork.[6]

Thus the pyrrolidine enamine[7] of 3-oxaquinolizidine,[8] III, was treated with one mole of acrylonitrile in ethanol to give, IV, b.p. 123° (0.2 mm.), picrate m.p. 179° (infrared spectrum shows nitrile at 2250 cm.$^{-1}$ and carbonyl at 1715 cm.$^{-1}$) which was further treated with pyrrolidine and thence a second mole of acrylonitrile in ethanol–dimethylformamide solution (1:1) and refluxed for 30 hr. After hydrolysis V was obtained as a thick yellow liquid, b.p. 145° (0.15 mm.), picrate m.p. 189–191° with decomposition (infrared shows intense nitrile band at 2250 cm.$^{-1}$ and carbonyl at 1715 cm.$^{-1}$).



III V

Compound V was hydrogenated in ethanol with W-5 Raney nickel catalyst at 1500 p.s.i. and 100° for 8 hr. The solvent was removed and the ether-soluble portion chromatographed on neutral alumina affording *dl*-matridine, I, m.p. (recrystallized from ethanol/acetone) 48–49°, picrate m.p. 229–232° with decomposition. The infrared spectrum was identical in every respect with *d*-matridine obtained by lithium aluminum hydride reduction of matrine. It was noted that no other ditertiary amines were isolated from the reduction. In addition to the resolution of *dl*-matridine we are now extending this approach to the synthesis of *dl*-matrine.

Acknowledgment.—The authors express their thanks to McNeil Laboratories, Incorporated, Philadelphia, and the National Institutes of Health (Research Grant A-2397) for their financial aid in this project.

DEPARTMENT OF CHEMISTRY
EMORY UNIVERSITY
ATLANTA 22, GEORGIA

LEON MANDELL
K. P. SINGH

RECEIVED DECEMBER 22, 1960

THE PREPARATION OF DIBORON TETRACHLORIDE FROM BORON MONOXIDE[1]

Sir:

Although boron monoxide has been known for several years,[2] there have been few investigations of its chemistry. We wish to report a new reaction of boron monoxide which also constitutes a unique and useful synthesis of diboron tetrachloride, B_2Cl_4. Stock[3] originally prepared diboron tetrachloride, B_2Cl_4, in small quantities by a discharge reaction in which the electrodes were immersed in liquid boron trichloride. Schlesinger and co-workers[4] have obtained diboron tetrachloride in higher yields by passing gaseous boron trichloride through a glow discharge between mercury electrodes at 1–2 mm. pressure. Subsequent modifications of this general discharge method utilizing gaseous boron trichloride have not resulted in significantly higher yields.[5,6,7]

Diboron tetrachloride now has been prepared conveniently by the reaction of boron trichloride with boron monoxide, $(BO)_n$, which was obtained by the vacuum dehydration of tetrahydroxydiboron as described previously.[8] Tetrahydroxydiboron

(1) The research reported in this document was supported by Wright Air Development Division, Air Research and Development Command, United States Air Force, under Contract AF 33(616)-5931.

(1) F. Bohlman, W. Weise, D. Rahtze and C. Arndt, *Ber.*, **91**, 2167 (1958).

(2) F. Bohlman, W. Weise, D. Rahtze and C. Arndt, *ibid.*, **91**, 2177 (1958).

(3) K. Tsuda, *et al.*, *Ber.*, **69**, 429 (1936); *J. Org. Chem.*, **21**, 1481 (1956).

(4) E. Ochai, S. Okuda and H. Minato, *J. Pharm. Soc. Japan*, **72**, 781 (1952).

(5) K. P. Singh and L. Mandell, Abs. A.C.S. meeting, Sept., 1960, p. 62.

(6) G. Stork, Abs. of the 16th National Organic Chemistry Symposium, June, 1959, pp. 44–52.

(7) G. Stork and H. K. Landesman, *J. Am. Chem. Soc.*, **78**, 5130 (1956).

(8) G. R. Clemo, T. P. Metcalfe and R. Raper, *J. Chem. Soc.*, 1429 (1936).

(2) E. Zintl, W. Morawietz and E. Gastinger, *Z. anorg. allgem. Chem.*, **245**, 8 (1940).

(3) A. Stock, A. Brandt and H. Fischer, *Ber.*, **58B**, 643 (1925).

(4) T. Wartik, R. E. Moore and H. I. Schlesinger, *J. Am. Chem. Soc.*, **76**, 5293 (1954).

(5) J. Frazer and R. Holzmann, *ibid.*, **80**, 2907 (1958).

(6) A. Holliday and A. Massey, *ibid.*, **80**, 4744 (1958).

(7) A. Holliday and A. Massey, *J. Chem. Soc.*, 43 (1960).

(8) T. Wartik and E. F. Apple, *J. Am. Chem. Soc.*, **77**, 6400 (1955).