propenyl radicals, e.g., (II), should have less resonance stabilization than the corresponding cations. The only evidence on this point to date is the observation[4] that (III), the dimer of (II), does not dissociate, but models show that (III) is relatively unhindered while steric repulsion in the dimer is a major factor in many dissociations to free radicals.[5] Accordingly it seemed necessary to seek other evidence on the stability of the three-pi-electron cyclic conjugated system.

We have determined the polarographic reduction potential of the triphenylcyclopropenyl cation and compared it with that of the triphenylmethyl cation (IV). Since the two compounds are of similar size and shape it is expected that the difference in reduction potentials will result chiefly from the loss of resonance energy when (Ia) is transformed to (II). Simple m.o. theory predicts that the reduction of (IV) results in no loss of resonance energy, although this is of course an approximation and our comparisons really indicate only the difference between the ΔD.E. for reduction of (Ia) and that for reduction of (IV). Other correlations between polarographic reduction potentials and calculated changes in delocalization energy have been found by a number of authors.[6]

Ia, R = R' = R'' = H
b, R = R' = H, R'' = OCH₃
c, R = R' = R'' = OCH₃

III

IV
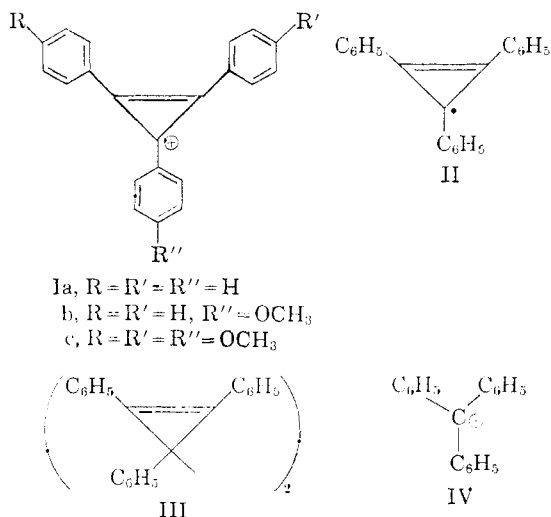
Since examination by d.c. polarography revealed that a reversible potential could not be obtained for (Ia) because of a rapid dimerization of the product (II), the technique of triangular wave potential oscillopolarography[7,8] was employed. Solutions 0.2 mM. in the cation perchlorates[9] were prepared in dry acetonitrile containing 0.1 M tetraethylammonium perchlorate, and the reference electrode was a silver wire in 0.1 M silver perchlorate in acetonitrile.[10] When (Ia) was examined at 10 c.p.s., only a cathodic wave was ob-

(4) R. Breslow and P. Gal, J. Am. Chem. Soc., 81, 4747 (1959).
(5) G. H. Wasserman in M. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 387.
(6) For reviews, cf. G. Holjtink, Chem. Weekblad, 56, 54 (1960); R. Daudel, R. Lefebvre and C. Moser, "Quantum Chemistry," Interscience Publishers, Inc., New York, N. Y., 1959, p. 276.
(7) J. Loveland and P. Elving, Chem. Revs., 51, 67 (1952).
(8) D. Smith and W. Reinmuth, unpublished work.
(9) All new compounds were fully characterized and their ionized state in solution was confirmed by ultraviolet spectroscopy.
(10) The potential of this reference electrode vs. the saturated calomel electrode is +0.380.

served, because of irreversible dimerization of the product radical, but at 150 c.p.s. the anodic and cathodic peak currents are equal, indicating that the radical can be reoxidized completely before dimerization. Using this technique the reversible reduction potential for (Ia) can be estimated as -1.132 ± 0.01 v., while that for (IV) is only -0.090 v. For (Ia) the dimerization is so rapid that d.c. polarography gives a value of -0.88 v., but in the case of (IV) the two methods agree, and high frequency oscillating potentials need not be employed to obtain the reduction potential uncomplicated by chemical kinetic processes. Using oscillopolarography we have also determined the reversible reduction potential of p-anisyldiphenyl cyclopropenyl cation (Ib) to be -1.24 v., while that of the corresponding trianisyl cation (Ic) is -1.49 v. Controlled potential coulometry of (Ia), (Ib), and (Ic) demonstrates that their reductions involve one electron, and the product from the reduction of (Ia) has been identified as (III). Analysis of the d.c. polarographic wave for (IV) indicates it undergoes a one-electron reduction.

It is obviously much more difficult to reduce the cyclopropenyl cations than it is to reduce the triphenylmethyl cation; if this difference is chiefly because of the loss of resonance energy resulting when the cyclopropenyl cations are converted to radicals, this corresponds to a loss of 1.04 e.v., or 24 kcal./mole, for (Ia) and of even more for the anisyl derivatives. This result roughly corresponds to the predictions of simple m.o. theory, in which ΔD.E.$_{red.}$ for (Ia) is predicted to be -0.504β while that for (IV) is predicted to be zero; the value of β appropriate to such changes has been suggested to be of the order of -2 e.v.[11] However, the agreement with simple m.o. calculations is by no means perfect, since from symmetry considerations it is predicted that the ΔD.E. for (Ib) should be precisely the same as that for (Ia); to accommodate the observed difference in reduction potentials, electron correlation must be considered.[11] The details of the relationship between m.o. calculations and observed reduction potentials in this series will be discussed in the full publication.

(11) A. Streitwieser, J. Am. Chem. Soc., 82, 4123 (1960).

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ANTIPARASITIC DRUGS. IV. 2-(4'-THIAZOLYL)-BENZIMIDAZOLE, A NEW ANTHELMINTIC

Sir:

We wish to report the discovery of a new class of anthelmintic agents possessing a broad spectrum of activity for gastrointestinal parasites of domestic animals. Some of the compounds are among the most potent chemotherapeutic agents known, complete larvacidal activity being manifest in vitro at 10^{-5} γ/ml.[1] This potency coupled with the absence of activity toward other microorganisms and negligible mammalian toxicity

(1) Phenothiazine under similar conditions is active at about 10^{-1} γ/ml. Penicillin against a sensitive staphylococcus has an end-point of about 3 × 10^{-3} γ/ml. Cf. H. Welch, "Antibiotic Therapy," The Arundel Press, Inc., Washington, D. C., 1951, p. 62.

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]
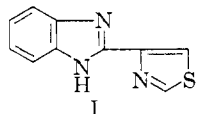
Compounds with substituents at positions C_1, C_2 and C_5 of the benzimidazole ring were synthesized and examined for anthelmintic activity. Treatment of the anion (sodium hydride in benzene–dimethylformamide) of I with methyl iodide gave the 1-methyl derivative of I, m.p. 139–140°, similarly 1-benzoyl 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.

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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].

(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.

(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).