COMMUNICATIONS TO THE EDITOR

SYNTHESIS OF COMPOUNDS IN THE THIOCTIC ACID SERIES

Sir:

The name "thioctic acid" was proposed for 5,8-dithioöctanoic acid, a biologically active compound,[1] and it was suggested that the number of the carbon atom to which the secondary sulfur is attached might be used to designate various compounds in this series. It has now become evident that the biological activity of 5-thioctic acid is much less than that of 6-thioctic acid (6,8-dithiooctanoic acid) which has been synthesized by a new method. The synthesis of thioctic acid from γ-(2-tetrahydrofuryl)-butyric acid was described.[2] Although this synthesis would be expected to yield primarily 5,8-dithioöctanoic acid, the possibility of producing other isomers by rearrangement was pointed out.[2] We have improved this synthesis and have isolated three isomeric compounds.

The expected DL-5-thioctic acid, m.p. 58° (calcd. for $C_8H_{14}O_2S_2$: neut. equiv., 206; C, 46.6; H, 6.8; S, 31.1. Found: neut. equiv., 207; C, 46.2; H, 7.0; S, 31.5) was isolated in 22% over-all yield from our original synthesis starting with γ-(2-tetrahydrofuryl)-butyric acid. A second isomer, m.p. 81–86° (found: mol. wt., 200 (Rast camphor); C, 46.7; H, 7.0; S, 31.6) was isolated in 1% yield. This product was the only compound isolated (7% yield) when 4-hydroxy-8-bromoöctanoic acid or its lactone was treated with hydrobromic acid and thiourea followed by alkaline hydrolysis and iodine oxidation. This isomer is presumed to be 4-thioctic acid.

The third isomer was formed in approximately 5% over-all yield as measured by bioassay and was obtained in pure form only after oxidation to the sulfoxide and conversion to the crystalline S-benzylthiuronium salt, m.p. 143–144°.[2] This pure salt was converted to the acid, reduced with sodium borohydride to the dithiol and reoxidized with iodine to the intramolecular disulfide. This third isomer has been shown to be DL-6-thioctic acid, since by X-ray diffraction studies the S-benzylthiuronium salt of the sulfoxide was identical with the corresponding salt of the sulfoxide prepared from a sample of DL-6-thioctic acid obtained by the following synthesis: ethyl adipyl chloride was condensed with ethylene in the presence of aluminum chloride to yield on distillation ethyl Δ^7,6-ketooctenoate, b.p. 116–118° at 1.5 mm. (I). Thioacetic acid was added to I and the mixture was then reduced with sodium borohydride in methanol and hydrolyzed to give DL-8-thiol-6-hydroxyoctanoic acid (II), b.p. 164° at 0.05 mm. II was converted to crude DL-6,8-dithioloctanoic acid (dihydro-6-thioctic acid) (III) by treatment with excess thiourea in refluxing 50% hydriodic acid followed by alkaline hydrolysis. Crude III was oxidized in dilute chloroform solution to the intramolecular disulfide, DL-6-thioctic acid (IV) with iodine in potassium iodide solution. The crude IV was purified by vacuum distillation, b.p. 160–165° at 0.1 mm., and recrystallization from cyclohexane, m.p. 60–61°; found: neut. equiv. 202; C, 45.08; H, 7.08; S, 30.84. The biological activities of these three thioctic acids are compared in Table I.

(1) J. A. Brockman, Jr., *et al.*, THIS JOURNAL, **74**, 1868 (1952).
(2) M. W. Bullock, *et al.*, *ibid.*, **74**, 1868 (1952).

TABLE I

BIOLOGICAL ACTIVITIES OF COMPOUNDS IN THE THIOCTIC ACID SERIES

Acid	Relative potency for *Streptococcus faecalis*[3]	Mμg per ml. of medium for half-maximum growth *Tetrahymena geleii*[4]	*Corynebacterium*[5]	Relative pyruvate oxidation factor activity[6]
DL-6-thioctic	100	0.376	0.5	100[a]
DL-5-thioctic	0.08	98	610	0.3
DL-4-thioctic	0.04	575	770	0.1

[a] In the test system employed 10 millimicrograms of DL-6-thioctic acid gave an oxygen uptake of 225, 290 and 259 microliters per hour on different days.

(3) F. P. Day, *et al.*, *Bacteriological Proceedings*, Soc. of Am. Bacteriologists, p. 136 (1951).
(4) By G. W. Kidder, Amherst College, Amherst, Mass.
(5) E. L. R. Stokstad, *et al.*, *Proc. Soc. Exp. Biol. Med.*, **74**, 571 (1950).
(6) I. C. Gunsalus, M. I. Dolin and L. Struglia, *J. Biol. Chem.*, **194**, 849 (1952).

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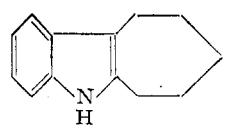
1-AZABENZ[b]AZULENE

Sir:

Treibs[1] recently described 1-azabenz[b]azulene (II), prepared by reaction of I with iodine and nitrobenzene, as a blue solid which was unstable to heat and light. The basic character of the substance and analysis (Cl, N) of its unstable hydrochloride constituted the only evidence for the structure of the product. No data identifying the starting material were given.

Prior to the publication of Treibs' results we had obtained II as a dark red solid (m.p. 140–141°) stable to heat and light and basic in character (soluble in aqueous acid).



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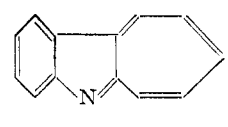

II

Our starting material (I) was prepared by the method of Rogers and Corson[2] and identified by its m.p. (140–141°),[3] preparation of a dark red

(1) v. W. Treibs, *Ann.*, **576**, 110 (1952).
(2) C. U. Rogers and B. B. Corson, THIS JOURNAL, **69**, 2910 (1947).
(3) N. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, 2583 (1928).