phenylhydrazide (II); m. p. 153.5–155.7° (cor.); $[\alpha]^{25}D$ 0.0° (3% in acetone). (I) was fractionally recrystallized from toluene to give 4.0 g. of N-carbobenzoxy-L-*o*-fluorophenylalanylphenyl-hydrazide (III); m. p. 171.0–172.0° (cor.); $[\alpha]^{25}D$ −31.0° (3% in acetone). *Anal.* Calcd. for $C_{23}H_{22}O_3N_3F$: C, 67.8; H, 5.4; N, 10.3. Found: C, 67.9; H, 5.7; N, 10.3; and 4.0 g. of (II); m. p. 155.5–156.5° (cor.); $[\alpha]^{25}D$ 0.0° (3% in acetone). *Anal.* Calcd. for $C_{23}H_{22}O_3N_3F$: C, 67.8; H, 5.4; N, 10.3. Found: C, 67.9; H, 5.6; N, 10.3. The filtrate from (II) was concentrated under reduced pressure, acidified, and the oily solid recrystallized from toluene to give 5.6 g. of an approximately equimolar mixture of N-carbobenzoxy-D-*o*-fluorophenylalanine and N-carbobenzoxy-DL-*o*-fluorophenylalanine. Fractional recrystallization from toluene gave 1.0 g. of N-carbobenzoxy-D-*o*-fluorophenylalanine (IV); m. p. 103–105° (cor.); $[\alpha]^{25}D$ +15.7° (5% in acetone). *Anal.* Calcd. for $C_{17}H_{16}O_4NF$: C, 64.3; H, 5.1; N, 4.4. Found: C, 64.4; H, 5.1; N, 4.2; and 1.9 g. of N-carbobenzoxy-DL-*o*-fluorophenylalanine (V); m. p. 108.5–110.0° (cor.); $[\alpha]^{25}D$ 0.2° (5% in acetone). *Anal.* Calcd. for $C_{17}H_{16}O_4NF$: C, 64.3; H, 5.1; N, 4.4. Found: C, 64.5; H, 5.3; N, 4.5.

A simultaneous enzymatic resolution of N-carbobenzoxy-DL-alanine using an aliquot of the same enzyme preparation gave N-carbobenzoxy-L-alanylphenylhydrazide in 75% yield after one recrystallization; m. p. 154.5–155.5° (cor.); $[\alpha]^{25}D$ −27.2° (5% in acetone).

Other experiments not reported here indicate that the behavior noted with *o*-fluorophenylalanine is not unique and it is clear that further study on the effect of the nature of the side chain, of the base, and of the acyl group on the course of the enzymatic synthesis is required. Such investigations are now in progress.

GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA, CALIFORNIA EDWARD L. BENNETT
CARL NIEMANN

RECEIVED JULY 6, 1948

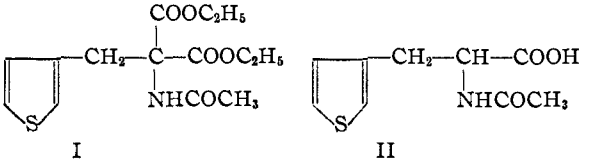
THE SYNTHESIS OF β-3-THIENYLALANINE

Sir:

Due to the current interest in metabolite–antimetabolite relations, and in particular to the discovery by du Vigneaud and associates[1,2] that β-2-thienylalanine functioned as a phenylalanine anti-metabolite with yeast, we are prompted to describe an isomer of this compound, β-3-thienylalanine, which we have prepared for testing as a phenylalanine antagonist.

The synthesis involves the reaction of 3-thienyl bromide with sodioacetamidomalonic ester to form 3-thenylacetamidomalonic ester (I). The 3-thenyl bromide was prepared by the peroxide-catalyzed reaction of N-bromosuccinimide with 3-methylthiophene, as previously described.[3] I melted at 90–91° after recrystallization from water.

Anal. Calcd. for $C_{14}H_{19}O_5NS$: S, 10.20. Found: S, 9.92. Alkaline hydrolysis of I, followed



I II

by acidification and heating, yielded N-acetyl-β-3-thienylalanine (II), m. p. 148–149°. *Anal.* Calcd. for $C_9H_{11}O_3NS$: S, 15.03; N, 6.57. Found: S, 15.14; N, 6.82.

β-3-Thienylalanine was prepared by complete hydrolysis of I in barium hydroxide, acidification with sulfuric acid, decarboxylation, and neutralization with barium carbonate. The water solution thus obtained was concentrated to dryness, and the residue recrystallized from water. β-3-Thienylalanine precipitated as fine white crystals, which browned at 260° and melted with decomposition from 265–267°. *Anal.* Calcd. for $C_7H_9O_2NS$: S, 18.71; N, 8.19. Found: S, 18.43; N, 8.10.

Complete details on the synthesis and biological testing of this compound will be published at a later date.

(3) Campaigne and LeSuer, THIS JOURNAL, **70**, 1555 (1948).

E. CAMPAIGNE
R. CLIFFORD BOURGEOIS
CHEMISTRY LABORATORY ROGER GARST
INDIANA UNIVERSITY WALTER C. MCCARTHY
BLOOMINGTON, INDIANA ROBERT L. PATRICK
HARRY G. DAY

RECEIVED MARCH 13, 1948

THE PREPARATION AND POLYMERIZATION OF MONOMERIC CYCLIC DISULFIDES

Sir:

Carothers extensively described the reversible polymerization relationships existing between monomeric cyclic anhydrides,[1] esters,[2] and formals.[3] Patnode and Wilcock[4] recently described the reversible conversion of methyl polysiloxanes to cyclic compounds. We have found that a similar reversible polymerization is possible between high-molecular weight disulfide polymers and the corresponding monomeric disulfide ring.

Steam distillation of aqueous dispersions of disulfide polymers yields very small amounts of

(1) du Vigneaud, McKennis, Simonds, Dittmer and Brown, *J. Biol. Chem.*, **159**, 385 (1945).

(2) Dittmer, Ellis, McKennis and du Vigneaud, *ibid.*, **164**, 761 1946).

(1) J. W. Hill and W. H. Carothers, THIS JOURNAL, **55**, 5023 (1933).

(2) W. H. Carothers, G. L. Dorough and F. J. Van Natta, *ibid.*, **54**, 761 (1932).

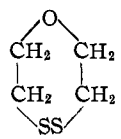
(3) J. W. Hill and W. H. Carothers, *ibid.*, **57**, 925 (1935).

(4) W. Patnode and D. F. Wilcock, *ibid.*, **68**, 358 (1946).

low-molecular weight organic compounds in the distillate. The rate of production of monomer is extremely slow but has not diminished with time, indicating that actually depolymerization is occurring. Addition of small amounts of sodium hydroxide to the polymeric dispersion significantly increases the rate of depolymerization.

The polymer resulting from the condensation of bis-(2-chloroethyl) ether and sodium disulfide[5] yields a pale yellow oil of characteristic odor. Attempts to distil it have resulted in decomposition. The compound is stable indefinitely if completely dry but water converts it slowly back to the original polymer. Aqueous sodium sulfide or polysulfide converts the oil rapidly to the polymeric form.

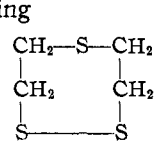
$$(-CH_2CH_2OCH_2CH_2SS-)$$
I


II

The physical properties of the oil were determined and compared with those calculated for structure II.

	Found	Calculated
Index of refraction $n^{20}D$	1.5823	...
Molecular refraction	36.7	36.3
Specific gravity	1.2737	...
Molecular weight	137	136
Sulfur, %	46.3	47.1

Cyclic compounds containing one or more heterocyclic sulfur atoms are well represented in the literature but heterocyclics with a disulfide group are not well known. Fromm and Joerg[6] reported on the ring



which they obtained by the reaction of $ClC_2H_4SSC_2H_4Cl$ with Na_2S or $ClC_2H_4SC_2H_4Cl$ with Na_2S_2. They reported a melting point of 74 to 75° for the product obtained by either method.

The production of polymer would appear more probable from this method of preparation than would the formation of a cyclic monomer. By substantially the same procedure, we have prepared polymeric products.

Cyclic compounds similar to that resulting from the ether disulfide have been obtained from disulfide polymers of different structures, but the products have yet to be characterized. A complete account of this work, together with theoretical considerations, will appear at a later date.

COMMUNICATION FROM THE THIOKOL CORPORATION TRENTON, N. J.
F. O. DAVIS
E. M. FETTES

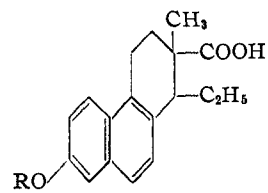
RECEIVED APRIL 20, 1948

(5) J. C. Patrick, *Trans. Faraday Soc.*, **32**, 347 (1946).
(6) Fromm and Joerg, *Ber.*, **58**, 304 (1925).

BIS-DEHYDRODOISYNOLIC ACID

Sir:

The substance I (R = H) has recently attracted considerable attention because it is one of the most potent estrogens known. In a series of brilliant studies Miescher, Heer and Billeter obtained I (R = H) both as a degradation product


I

of natural equilenin and by total synthesis.[1] More recently Anner and Miescher[2] announced an improved synthesis involving about ten steps from 1-aminonaphthalene-6-sulfonic acid (Cleve's acid) to the methyl ether I (R = CH_3). We wish to disclose herewith a facile total synthesis of this substance utilizing the Stobbe condensation of diethyl succinate with 2-propionyl-6-methoxynaphthalene (readily available by Friedel–Crafts acylation of β-naphthyl methyl ether[3]). Catalytic hydrogenation of the resulting condensation product over platinum oxide gave β-carboxy-γ-(6-methoxy-2-naphthyl)-caproic acid (m. p. 157–158°, dec. *Anal.* Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.30; H, 6.30) which on cyclization *via* the anhydride with aluminum chloride in nitrobenzene produced 1-ethyl-4-keto - 7 - methoxy - 1,2,3,4 - tetrahydrophenanthrene-2-carboxylic acid, m. p. 215.5–216.5° (*Anal.* Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.31; H, 6.03). Hydrogenation of the keto acid over palladium-on-charcoal catalyst in the presence of a trace of perchloric acid gave 1 - ethyl - 7 - methoxy - 1,2,3,4 - tetrahydrophenanthrene-2-carboxylic acid, m. p. 203.5–206°. (*Anal.* Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.36; H, 7.07), which on treatment in ether solution with diazomethane followed by sodium triphenylmethyl and methyl iodide afforded upon hydrolysis normal bis-dehydrodoisynolic acid methyl ether I (R = CH_3), m. p. 230–231° alone or when mixed with an authentic specimen of the same melting point which was kindly supplied by Dr. C. R. Scholz of Ciba Pharmaceutical Products. The methyl ester of I (R = CH_3) melted at 74.5–76.5° and gave no melting point depression on admixture with the ester (m. p. 75–76.5°) prepared from authentic I (R = CH_3).

Bioassays kindly performed by Drs. R. K. Meyer and E. G. Shipley of the University of Wisconsin Zoology Department showed our acid

(1) Miescher, *Helv. Chim. Acta*, **27**, 1727 (1944); Heer, Billeter and Miescher, *ibid.*, **28**, 991, 1342 (1945).
(2) Anner and Miescher, *Helv. Chim. Acta*, **29**, 586 (1946).
(3) Haworth and Sheldrick, *J. Chem. Soc.*, 864 (1934).