washings were boiled down to a thick oil. This product was recrystallized from ligroin, the separation of unreacted, ligroin-insoluble acetylsalicylic acid being conveniently carried out in the same operation. Further recrystallization from dioxane–water and pyridine–water gave 24.5 g. (36%) of N-(acetylsalicyloyl)-piperidine in the form of white needles, m. p. 145–146°. *Anal.* Calcd. for $C_{14}H_{17}NO_3$: N, 5.66. Found: N, 5.51.

NUTRITION RESEARCH LABORATORIES
CHICAGO 30, ILLINOIS ARTHUR J. TOMISEK

RECEIVED MAY 10, 1948

COMMUNICATIONS TO THE EDITOR

DESTHIOBENZYLPENICILLIN

Sir:

"From the standpoint of organic chemistry, the most convincing evidence"—for the lactam formula of benzylpenicillin—"was secured by a study carried out in the Merck laboratories of the action of Raney nickel catalyst upon sodium benzylpenicillinate." A monocarboxylic acid $C_{16}H_{20}O_4N_2$ benzyldesthiopenicillin and phenylacetyl-L-alanyl-D-valine were obtained.[1] Through the kindness of Dr. Ellis V. Brown and Mr. John L. Smith of Chas. Pfizer and Co., Inc., we were given an ample supply of sodium benzylpenicillinate and have studied its desulfurization with the active W-6 Raney nickel catalyst.[2]

It proved possible to remove the sulfur from sodium benzylpenicillin in alcohol at about 15° under 5000 p. s. i. of hydrogen, within one or two hours. However, under these conditions the phenyl group is hydrogenated to cyclohexyl, to some extent. The preferred procedure has been to carry out the desulfurization in 96% alcohol under about 45 p. s. i. of hydrogen for a period of four hours at 10–20°. The reaction appears to be complete after an hour or two.

Eleven desulfurizations, each on 500 mg. of sodium benzylpenicillinate with 16 g. of W-6 Raney nickel, have been carried out under the preferred conditions. A crude product was obtained by extracting with chloroform the reaction mixtures, made acid to *p*H 2, after the removal of the catalyst and alcohol. Chloroform soluble neutral products were then removed by converting the desthiobenzylpenicillin to its salt and extracting the alkaline solution with chloroform. The desired acid was then obtained by extraction of the acidified solution with chloroform. The average weight of crude desthiobenzylpenicillin obtained was 220 mg. This product is free of basic or neutral compounds and of those containing sulfur. After crystallization from an alcohol–water mixture, the average yield of product, m. p. above 100°, was 150 mg. from seven desulfurizations. In four cases where the product so obtained was recrystallized, there was obtained 120–130 mg. of desthiobenzylpenicillin, m. p. 106–109°, 108–110°, 108.5–110.5° and 110–113°. The product shows a neutral equivalent and analyses corresponding to the molecular formula given above.

These results, obtained under so mild conditions of reaction, support the conclusion of Kaczka, Mozingo and Folkers of the Merck laboratories that an intramolecular rearrangement is not involved in the formation of desthiobenzylpenicillin.

LABORATORY OF ORGANIC CHEMISTRY HOMER ADKINS
UNIVERSITY OF WISCONSIN FRED J. BRUTSCHY[3]
MADISON, WISCONSIN MARGARET MCWHIRTER

RECEIVED FEBRUARY 16, 1948

(1) *Science*, **105**, 657 (1947).

(2) Adkins and Billica, THIS JOURNAL, **70**, 695 (1948).

(3) Du Pont Post-doctorate Fellow 1946–1947.

THE ENZYMATIC SYNTHESIS OF N-CARBOBENZOXY-D AND L-*o*-FLUOROPHENYLALANYLPHENYLHYDRAZIDES

Sir:

Previous studies on the resolution of acylated DL-amino acids by the asymmetric enzymatic synthesis of the anilide or phenylhydrazide of the acylated L-amino acid[1] have given no indication that appreciable quantities of the anilide or phenylhydrazide of the acylated D-amino acid may also be formed. We wish to report a case where substantial quantities of the D-phenylhydrazide have been synthesized despite the fact that the amount of amine present was insufficient to permit quantitative conversion of both the D- and L-acids.

25.0 g. (0.079 mole) of N-carbobenzoxy-DL-*o*-fluorophenylalanine was incubated with 20 g. of activated papain, 36.0 g. of L-cysteine hydrochloride, and 4.3 g. (0.040 mole) of redistilled phenylhydrazine at 40° for five days. The precipitated N-carbobenzoxy-*o*-fluorophenylalanylphenylhydrazide was recovered and recrystallized from toluene to give 11.0 g. of N-carbobenzoxy-*o*-fluorophenylalanylphenylhydrazide (I); m. p. 152–160°; 5.0 g. of additional papain, 12.0 g. of cysteine hydrochloride and 1.00 g. of phenylhydrazine was added to the filtrate from (I), the solution was incubated for five days at 40°, and the precipitate recrystallized from toluene to give 3.0 g. of N-carbobenzoxy-DL-*o*-fluorophenylalanyl-

(1) M. Bergmann and H. Fraenkel-Conrat, *J. Biol. Chem.*, **119**, 707 (1937).

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

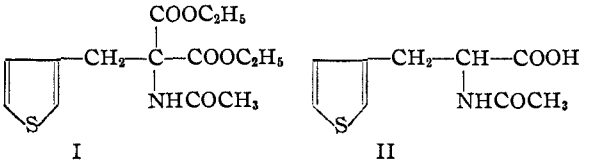
THE SYNTHESIS OF β-3-THIENYLALANINE

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).

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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).