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.

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RECEIVED FEBRUARY 16, 1948

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[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-

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