Experimental

Acylation of Kojic Acid (I).—Twenty grams (0.142 mole) of kojic acid was mixed with 125 g. (1.22 moles) of acetic anhydride and 10 g. of zinc chloride. The mixture was heated over a water-bath under reflux and protected from moisture with a calcium chloride tube until the first vigorous reaction had subsided. The water-bath was then removed and replaced with an oil-bath. The heating was continued by gradually increasing the temperature to 145°, and then maintaining the temperature between 135–145° for one and one-half hours. Upon completion of the heating of the mixture, the excess acetic anhydride and acetic acid were removed under reduced pressure.

The residue was then treated with 200 ml. of boiling water and set aside to cool. After cooling, the crystals were filtered off. The filtrate was extracted with three successive 100-ml. portions of benzene. The combined benzene fractions were added to the crystals, which immediately dissolved. The mixture was washed once with cold water, dried with anhydrous magnesium sulfate, and decolorized with Norite.

The benzene was allowed to evaporate and 24.8 g. of a pale yellow compound were obtained. The substance was recrystallized by dissolving it in the smallest quantity of boiling water necessary to obtain complete solution (500–600 ml.). The white compound thus obtained was air dried. The analytical sample was dried in the vacuum desiccator over sulfuric acid for three weeks, m. p. 106°. The compound was quite soluble in ether, alcohol, benzene and ethyl acetate as well as hot water.

Anal. Calcd. for $C_{10}H_{13}O_7$: C, 48.98; H, 5.30; mol. wt., 245. Found: C, 49.06, 49.28, 49.10; H, 5.39, 5.72, 5.62; mol. wt. 248. (Each of the three carbon–hydrogen analyses was on a sample from a different run.[2])

Impure samples of the compound always gave a faint red color with dilute ferric chloride solutions; however, the pure samples failed to give the test. The compound did not react with dilute sodium bicarbonate solution. When 1.6137 g. of the ketone was heated ten hours in the electric drying oven at a temperature of 100–102° it lost 0.0376 g. (2.31%) of its weight, one molecule of water would require a loss of 7.34%. This loss of weight, perhaps, cannot be entirely attributed to the loss of moisture because the material developed a faint odor at this temperature.

The 2,4-dinitrophenylhydrazine derivative of compound (I) had a melting point of 114°.

Anal. Calcd. for $C_{10}H_{13}O_3$ $(C_6H_4N_4O_4)_4$: N, 23.21. Found: N, 23.18, 23.40.

Hydrolysis of Compound (I) to Form Compound (II).—A small portion (1 g.) of purified compound (I) dissolved in 50 ml. of hot water was refluxed for fifteen hours. The solution was cooled, decolorized with a little Norite, and filtered. After the water was evaporated and the solid dissolved in absolute ethanol, the solvent was removed under reduced pressure; and the compound was completely dried in the vacuum desiccator. The compound was a colorless glassy material which had a m. p. of 55–57°. Its semicarbazide had a m. p. of 247°. The compound was very soluble in water and in alcohol, but insoluble in acetone and ether. The material was not acidic and did not give any color with dilute ferric chloride solution.

Anal. Calcd. for $C_8H_{11}O_6$: C, 47.29; H, 5.41. Found: C, 47.50; H, 5.84.

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RECEIVED FEBRUARY 24, 1948

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[2] Analyses by Dr. Carl Tiedcke.

NEW COMPOUNDS

Esters of Mucic Acid

The new compounds[1] listed in Table I were prepared by refluxing and stirring mechanically a mixture of 50 g. of mucic acid and 500 g. of the corresponding alcohol in the presence of 2 g. of *p*-toluenesulfonic acid. The esters all crystallized directly from the cooled reaction mixtures, after removal of unreacted mucic acid by filtration, and were recrystallized from 95% ethanol.

TABLE I

ESTERS OF MUCIC ACID

Di-esters	M. p., °C.	Yield. %	Formula	Analyses Carbon, % Calcd.	 Found	 Hydrogen, % Calcd.	 Found	 Sapon. equiv. Calcd.	 Found
n-Propyl	149–150	48	$C_{12}H_{22}O_8$	48.98	48.9	7.54	7.64	147.1	146.8
n-Butyl	142.5–143.5	93	$C_{14}H_{26}O_8$	52.16	52.2	8.13	8.17	161.2	160
n-Amyl	147–147.5	74	$C_{16}H_{30}O_8$	54.84	54.9	8.63	8.68	175.2	174.2
n-Hexyl	143–144	55	$C_{18}H_{34}O_8$	57.12	57.0	9.06	8.94	189.2	189.1
Allyl	156.5–158	78	$C_{12}H_{18}O_8$	49.65	49.6	6.25	6.35	145.1	145.6

The *n*-propyl and *n*-butyl mucates were prepared by refluxing the reaction mixtures for thirty and ten hours, respectively. The *n*-amyl and *n*-hexyl esters were prepared in essentially the same manner except that 200 g. of xylene was added to the mixture, which was refluxed under a Bidwell–Sterling water trap for twenty and forty hours, respectively. In the preparation of allyl mucate, 250 g. of benzene was added, and refluxing and stirring continued for thirty hours, after which benzene, allyl alcohol and water were slowly distilled through a fractionating column until the final reaction solution was approximately 150 ml.

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[1] Dimethyl and diethyl mucates were prepared by Fischer and Speir (*Ber.*, **28**, 3252 (1895)), the former by reaction of mucic acid and methanol–hydrochloric acid in a sealed tube at 100° and the diethyl ester by refluxing mucic acid with ethanol and hydrochloric acid.

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RECEIVED FEBRUARY 16, 1948

N-(Acetylsalicyloyl)-piperidine

Fifty grams of acetylsalicylic acid and 250 ml. of thionyl chloride were refluxed for two hours. Excess thionyl chloride was removed on a steam-bath and with vacuum. The residue was taken up in dry benzene and a solution of 55 ml. (100% excess) of piperidine in dry benzene was added cautiously and with cooling. After filtering off the piperidine hydrochloride, the combined liquors and 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.

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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

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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).