An ether solution of the dihydrate was treated with phosphorus pentoxide, and samples taken at intervals during a twenty-four-hour period were tested for the presence of hexafluoroacetylacetone.[4] Upon standing for a short time, no test for the hexafluoroacetylacetone was obtained, although after twenty-four hours an immediate test was obtained. The dehydration process progressed rapidly when an ether solution of the dihydrate was refluxed over phosphorus pentoxide for one hour, and then fractionally distilled. The fraction coming over above 35° gave an immediate test for the diketone.

Similarly, an increase in the *p*H of an aqueous solution resulted in a shift of the equilibrium to the right. Thus, an aqueous solution which had been brought up to a *p*H of 7 with 0.1 *N* sodium hydroxide, when treated with a copper acetate solution, gave immediately the ether extractable derivative.

The equilibrium could also be reversed as evidenced by the fact that when an ethereal solution of the hexafluoroacetylacetone was shaken with water, an immediate test for the diketone could not be obtained.

(4) The presence of hexafluoroacetylacetone was determined by shaking the test solution with aqueous copper acetate. The appearance of a green ethereal layer was taken as evidence of the formation of bis-(1,1,1,5,5,5 hexafluoro-2,4-pentanediono)-copper. This was confirmed by analyses of such copper derivatives recovered by evaporation of the ether solution. *Anal.* Found Cu, 13.4; F, 46.7; m. p. 114–116°. Calcd. Cu, 13.3; F, 47.8; m. p. 113–115°.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF WISCONSIN
MADISON 6, WISCONSIN

RECEIVED MAY 5, 1949

Resolution of DL-Tryptophan

BY A. C. SHABICA[1] AND MAX TISHLER

Although a number of excellent methods for the preparation of DL-tryptophan have been reported,[2] no equally satisfactory procedure for the resolution of the DL-mixture is known. We wish to report[3] a method of resolution developed by us several years ago which is simpler than the chemical procedures already reported.[4]

In this method N-acetyl-DL-tryptophan, an intermediate in a few of the recent syntheses, is resolved by brucine. The brucine salt of N-acetyl-D-tryptophan separates cleanly from ethanol and the L- form is obtained from the mother liquor. The N-acetyl enantiomorphs are hydrolyzed to the optically active amino acids by heating with 2*N* hydrochloric acid for about two hours. Both D- and L-tryptophan can be obtained in pure form and in good yields.

Brucine Salt of D- and L-N-Acetyltryptophan.—A mixture of 123 g. of N-acetyl-DL-tryptophan, 208 g. of brucine and 1750 cc. of absolute ethanol was boiled under reflux until solution was effected. After cooling, seeding and storing for twelve hours, the crystalline product was separated and slurried twice with small quantities of ethanol: Weight of dried product, 161 g.; $[\alpha]^{25}D$ − 16.5 ± 1°. Recrystallization from 320 cc. of hot ethanol gave 146 g. of pure brucine salt of N-acetyl-D-tryptophan ($[\alpha]^{25}D$ − 18.4°) as was indicated by its constant rotation when subjected to further recrystallization.

The brucine salt of N-acetyl-L-tryptophan was obtained from the resolution mother liquor by concentration of the solution to dryness under reduced pressure, dissolution of the residue in 320 cc. of hot methanol, charcoal treatment of the solution, dilution of the latter with 325 cc. of dry ether, seeding and storage of the mixture for several hours. The crystalline brucine salt was subjected again to the same recrystallization procedure whereby 139 g. of product was obtained; $[\alpha]^{25}D$ + 1.3 ± 1° (*c*, 1% in water). *Anal.* Calcd. for $C_{36}H_{40}O_7N_4$: C, 67.48; H, 6.29; N, 8.74. Found: C, 67.54; H, 6.13; N, 8.69.

L- and D-Tryptophan.—To a mixture of 49 g. of the recrystallized brucine salt of N-acetyl-L-tryptophan in 170 cc. of water was added 70 cc. of cold 1*N* sodium hydroxide solution. The salt dissolved readily and very soon brucine separated. After cooling in ice for a few hours, the mixture was filtered and the brucine washed with cold water. The combined filtrate and washings were neutralized with hydrochloric acid to *p*H 7.0, concentrated under reduced pressure to 140-cc. volume, treated with charcoal and finally acidified with hydrochloric acid *p*H 3.0. The N-acetyl-L-tryptophan was collected and slurried twice with cold water; weight 16.1 g. (85% yield); $[\alpha]^{25}D$ + 29° (*c*, 1% in H_2O + 1 equivalent NaOH).

A mixture of the product with 160 cc. of 2*N* hydrochloric acid was boiled under reflux for two and one-half hours and the resulting solution was concentrated under reduced pressure to dryness. The residue was dissolved in 40 cc. of hot water and the solution was treated with charcoal. A solution of 7 g. of sodium acetate in 20 cc. of water was added to the product solution and the mixture was stored at 5° for fourteen hours. The product was recrystallized by dissolution in 84 cc. of water containing 2.8 g. of sodium hydroxide, acidifying the warmed solution (at 70°) with 4.5 cc. of acetic acid and storing the mixture at 5° for fourteen hours. The pure L-tryptophan was collected and washed with small amounts of 50% ethanol followed by ethanol and then dry ether; weight, 10.9 g.; 82% yield; $[\alpha]^{25}D$ −31.90 (*c*, 1% in water + 1 equivalent of NaOH).

D-Tryptophan was obtained from the brucine salt of its N-acetyl derivative following the same procedure. The over-all yields were slightly better, however.

(1) Present address: Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

(2) Snyder and Smith, THIS JOURNAL, **66**, 350 (1944); Albertson, Archer and Suter, *ibid.*, **66**, 500; **67**, 36 (1945); Howe, Zambito, Snyder and Tishler, *ibid.*, **67**, 38 (1945); Lyttle and Weisblat, *ibid.*, **69**, 2118 (1947); Warner and Moe, *ibid.*, **70**, 2765 (1948).

(3) The procedure is reported at this time because of a number of recent requests for our method of effecting resolution of DL-tryptophan.

(4) du Vigneaud and Sealock, *J. Biol. Chem.*, **96**, 511 (1932); Berg, *ibid.*, **100**, 79 (1933).

RESEARCH LABORATORIES
MERCK & CO., INC.
RAHWAY, NEW JERSEY

RECEIVED JULY 27, 1949