TABLE I

DISSOCIATION OF AMMONIUM HYDROTELLURIDE

Pressure, mm.			Temp., °C.	$K_p \times 10^5$ (p in atm.), av.
9.9	9.9	10.0	2.5	4.2
10.7	10.6	10.7	5.0	5.0
13.3	13.0	13.2	10.0	7.5
16.3	16.0	16.2	15.0	11.3
19.9	20.0	19.7	20.0	17.1
22.7	23.0	22.9	25.0	22.7

sistent results due to the rapid rate at which H_2Te decomposes. The extent to which the decomposition proceeded could not be determined quantitatively.

It was difficult to obtain an accurate analysis on the small amount of solid formed from the reaction between ammonia and hydrogen telluride. The indirect method used in the previous paper could not be used because of the difficulty of handling H_2Te without complete decomposition. The assumption that the product was NH_4HTe is supported by the fact that both NH_4HS and NH_4HSe are formed by the reaction between ammonia and the corresponding hydride at the temperatures used in this work. Bineau[4] stated that he obtained ammonium hydrotelluride under similar conditions.

A plot of log K_p *vs.* $1/T$, gives a straight line, indicating that the data herein presented satisfy the requirements of van't Hoff's equation. The slope of the line is $-2{,}792$, hence ΔH for the dissociation is 12,280 calories within the indicated temperature range. ΔF at 25° is 4,972 cal./mole and ΔS 24.5 cal./mole/degree K. Using thermodynamic constants from Latimer[5] and the data above, constants were obtained, for 25°, for NH_4HTe: $\Delta H_f^0 = 10{,}900$ cal., $\Delta F_f^0 = 22{,}090$ cal., and $\Delta S_f^0 = -37.6$ e. u.

(4) Bineau, *Ann. chim. phys.*, **67**, 230 (1838).

(5) W. L. Latimer, "Oxidation Potentials," Prentice-Hall, Inc. (1938).

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The Synthesis of 5-Fluoro-DL-tryptophan

BY HEINRICH RINDERKNECHT[1] AND CARL NIEMANN[2]

The results obtained in metabolic and toxicity studies based upon the use of the various nuclear substituted monofluoro-phenylalanines and tyrosines[3] have been sufficiently enlightening to justify the extension of this program to include the fluorine derivatives of other naturally occurring α-amino acids. As a step toward this end we wish to report the synthesis of 5-fluoro-DL-tryptophan, a compound of particular interest as a metabolic antagonist in view of the manifold functions of the parent amino acid. The synthesis was patterned after the DL-tryptophan synthesis described by Warner and Moe.[4]

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(3) These studies are being conducted in collaboration with Dr. H. K. Mitchell of this Institute. For a preliminary account see THIS JOURNAL, **68**, 1671 (1946); **69**, 1232 (1947)

Experimental[5]

***p*-Fluorophenylhydrazine.**[6,7]—*p*-Nitrophenyldiazonium fluoroborate (35.0 g.) prepared as described previously[6,7] was suspended in 50 ml. of mineral oil, the decomposition initiated by heating with a free flame, the reaction mixture steam distilled and the distillate fractionally distilled to give 10.75 g. (52%) of *p*-nitrofluorobenzene, b. p. 97.5° at 15 mm. To a suspension of 3 g. of 7% palladized acid washed Norite in 100 ml. of methanol and 5 ml. of concd. hydrochloric acid was added 12.23 g. of *p*-nitrofluorobenzene, the mixture reduced with hydrogen at 25° and atmospheric pressure, the catalyst removed, 10 ml. of concd. hydrochloric acid added to the filtrate, the solvents and excess hydrogen chloride removed by repeated distillations the residue suspended in 100 ml. of hot acetone, sufficient methanol added to form a single phase, and the solution cooled to give 11.60 g. (91%) of *p*-fluoroaniline hydrochloride, m. p. 253° with dec.

Anal. Calcd. for C_6H_7NFCl (147.6): Cl, 2.4. Found: Cl, 2.4.

The amine was converted into the hydrazine as directed by Schiemann and Winkelmueller.[7] The yield of *p*-fluorophenylhydrazine hydrochloride was 80% and the free base, b. p. 133–134° at 25 mm., was obtained from the hydrochloride in 84% yield. The b. p. of the free base is reported[7] to be 133° at 25 mm. and 129.2° at 21 mm.

***p*-Fluorophenylhydrazone of γ-Acetamido-γ,γ-dicarbethoxybutyraldehyde** (I).—To the reaction product obtained from 13.2 g. of acetamidomalonic ester, 0.075 g. of sodium methoxide, and 4.15 ml. of redistilled acrolein in 19 ml. of benzene[8] was added 2.1 ml. of glacial acetic acid and 7.6 g. of *p*-fluorophenylhydrazine and the reaction conducted essentially as described previously[8] to give 13.9 g. (61%) of crude I. Crude I was recrystallized successively from aqueous ethanol and ethanol to give I, m. p. 105–106°.

Anal. Calcd. for $C_{18}H_{24}O_5N_3F$ (381.4): C, 56.8; H, 6.3; N, 11.0. Found: C, 56.7; H, 6.3; N, 11.0.

Ethyl α-Acetamido-α-carbethoxy-β-(5-fluoro-3-indole)-propionate (II).—Crude I (11.9 g.) was cyclized with aqueous sulfuric acid[4] (heated for two hours) to give 10.1 g. (89%) of crude II, m. p. 130–132°. Repeated recrystallization of a portion of crude II from ethanol gave II, m. p. 137–138°.

Anal. Calcd. for $C_{18}H_{21}O_5N_2F$ (364.4): C, 59.3; H, 5.8; N, 7.7. Found: C, 59.3; H, 5.8; N, 7.7.

α-Acetamido-α-carboxy-β-(5-fluoro-3-indole)-propionic Acid (III).—Saponification[9] of II (3.0 g.) gave 2.3 g. (91%) of III, m. p. 163° with decomp. after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{14}H_{13}O_5N_2F$ (308.2): N, 9.1. Found: N, 9.1.

Acetyl-5-fluoro-DL-tryptophan (IV).—A 10% aqueous solution of III was heated for two hours at the refluxing temperature and the solution cooled to give IV, m. p. 189–192° after two recrystallizations from ethanol.

Anal. Calcd. for $C_{13}H_{13}O_3N_2F$ (264.2): C, 59.0; H, 5.0; N, 10.6. Found: C, 59.1; H, 4.9; N, 10.6.

5-Fluoro-DL-tryptophan (V).—The saponification of IV with aqueous sodium hydroxide[9] gave preparations of V which were grossly contaminated with inorganic constitu-

(4) D. T. Warner and O. A. Moe, *ibid.*, **70**, 2765 (1948).

(5) All melting points are corrected.

(6) G. Schiemann and R. Pillarsky, *Ber.*, **62**, 3035 (1929).

(7) G. Schiemann and W. Winkelmueller, *ibid.*, **66**, 727 (1933).

(8) O. A. Moe and D. T. Warner, THIS JOURNAL, **70**, 2763 (1948).

(9) H. R. Snyder and C. W. Smith, *ibid.*, **66**, 350 (1944).

ents, probably silicates. The necessity of devising methods for the purification of the above products was eliminated when it was found that acetyl-DL-tryptophan could be hydrolyzed to DL-tryptophan in practically quantitative yields by heating aqueous solutions of the acetyl compound at 200° for six to seven hours. The following procedure was used for the conversion of III to V. III (1.5 g.) was heated with 20 ml. of water, contained in an unsealed bomb tube, at the refluxing temperature for 30 min., the tube was sealed, the tube and contents heated at 200° for six to seven hours, the hydrolysate decolorized with Norite, evaporated to dryness *in vacuo*, and the residue dried over phosphorus pentoxide. The residue was extracted with 15 ml. of boiling ethanol to give 0.88 g. (84%) of V, dec. p. 262–264°. This product was recrystallized from 30% aqueous ethanol to give V, dec. p. 264–265°.

Anal. Calcd. for $C_{11}H_{11}O_2N_2F$ (222.2): C, 59.5; H, 5.0; N, 12.6. Found: C, 59.4; H, 5.0; N, 12.6.

A small amount of IV was recovered from the ethanol extract.

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Studies on Nitrogen Trichloride Treated Prolamines. IV. Isolation of the Neurotoxic Principle

BY L. REINER, F. MISANI, T. W. FAIR, P. WEISS AND M. G. CORDASCO

In a recent publication Bentley, *et al.*,[1] announced the isolation of the toxic factor from nitrogen trichloride treated zein. We have also succeeded in isolating the toxic principle in a crystalline form and the purpose of this note is to report the procedure used and to describe the progress made in the characterization of this material.

The treatment of zein and the initial steps of purification with cation exchanger (Duolite C_1) were those reported previously.[2] For further purification the following procedure was adopted: The material (toxicity 0.5 g./kg.)[3] was hydrolyzed by refluxing with 5 *N* hydrochloric acid for four hours. After removal of the acid it was extracted repeatedly with butanol from an aqueous solution containing 5% trichloroacetic acid. Subsequently, it was precipitated at an acid *p*H value with mercuric acetate, the mercury and hydrogen sulfide removed and the concentrated solution treated with picric acid. In some instances a second mercury precipitation was carried out after removal of the picric acid. This was followed by treatment with Duolite to bring the *p*H to 3.7. The material dried *in vacuo* possessed a toxicity of about 30 mg./kg. The solid was extracted with hot methanol. On concentrating and cooling the methanol solution solids appeared, which after crystallization from aqueous methanol were toxic at 5 mg./kg. Recrystallization from water yielded rod-shaped crystals (see Fig. 1). They produced typical convulsions in rabbits at a dose of 1–1.5 mg./kg. and in mice by intraperitoneal injection at about 40 mg./kg. The material decomposed slowly at 220° and more rapidly at 240° without melting completely up to 350°.

Fig. 1.

The Pauly and biuret tests were negative. The compound contained sulfur but no –SH, –SS– or chlorine. A bluish purple dye was formed with ninhydrin. Paper chromatograms (ascending) revealed a single spot with R_f values of 0.04, butanol–acetic acid; 0.30, lutidine–collidine–ethanol; 0.62, phenol. After refluxing with 2 *N* sodium hydroxide for twenty-four hours the reaction with ninhydrin was negative. Refluxing for twenty-four hours with 5 *N* hydrochloric acid yielded two additional spots and almost complete destruction of the toxicity. There was, however, no increase in the alpha amino nitrogen content after hydrolysis[4] and no liberation of ninhydrin-positive material after hydrolysis of the dinitrophenyl derivative.

Analysis by Dr. Richard Baltzly (Wellcome Research Laboratories) gave C, 33.31; H, 6.57; N, 15.65; S, 16.15.[5] A compound having the formula $C_5H_{12}N_2O_3S$ calculates for C, 33.32; H, 6.71; N, 15.55; S, 17.79; mol. wt., 180.2. Molecular weight determination by freezing point lowering of water gave the value of 187. Electrometric titration revealed only two ionizing groups between the *p*H values of 2.0 and 9.5 having the *pK* values of 2.5 and 8.4, respectively; thus only one of the nitrogens is present as a free amino group. The

(1) Bentley, McDermott, Pace, Whitehead and Moran, *Nature*, **164**, 438 (1949).

(2) Reiner, Weiss, Misani, Cordasco and Fair, *Federation Proc.*, **8**, 241 (1949).

(3) Toxicity values reported in this communication were obtained in rabbits, orally, unless stated otherwise.

(4) Determined by Dr. James B. Allison, Rutgers University.

(5) The low sulfur value may be due to a slight contamination by sulfur-free amino acids. Analysis of a second batch was in agreement with the first, except that sulfur was higher, S, 17.81.