results in the precipitation of additional quantities of the carboxylic acid but the crude product is invariably mixed with some of the sodium complex. Furthermore, if the pure acid is half-neutralized with sodium hydroxide it can be reconverted to a complex which melts at 129.5–132°. This complex appears to be less stable than the analogous DL-complex since numerous attempts at recrystallization led to partial decomposition. These partially decomposed materials have the melting points of 126–128° reported by Bergmann[3] and Smith.[4]

The effect of other blocking groups and cations on the complex formation were examined briefly. Formyl-DL-phenylalanine and a dipeptide derivative (benzyloxycarbonylglycyl-L-phenylalanine) also exhibit the ability to form complexes. In the case of benzyloxycarbonyl-DL-phenylalanine, it was possible to isolate a solid potassium containing complex but the analogous lithium compound was obtained as a mixture of oil and solid.

EXPERIMENTAL[7,8]

Preparation of benzyloxycarbonyl-DL-phenylalanine and isolation of the complex. Benzyloxycarbonyl-DL-phenylalanine was prepared according to the standard procedure.[9] The crude product was dissolved in 550 ml. of hot ethyl acetate. On storage, 2.0 g. of a substance crystallized, m.p. 168–170°. Concentration of the filtrate to 75 ml. yielded an additional 4.1 g., m.p. 168–169.3°. Further concentration of the filtrate gave only benzyloxycarbonyl-DL-phenylalanine, m.p. 101–103.6°.

The combined 6.1 g. of high melting material was recrystallized several times from ethyl acetate, m.p. 168.5–169°.

Anal. Calcd. for $C_{34}H_{33}N_2O_8Na$: C, 65.89; H, 5.36; N, 4.51; Na, 3.70; mol. wt. 620.6; neut. equiv. 620.6. Found: C, 65.68; H, 5.53; N, 4.76; Na, 3.76; mol. wt. 656 (isothermal distillation in methanol); neut. equiv. 622.

Benzyloxycarbonyl-L-phenylalanine was prepared in the usual manner,[3] with the following modification. Rather than precipitating the product as a solid by acidification, the alkaline solution was acidified and extracted with ether. The ethereal solution was then washed with 2*N* hydrochloric acid, water, dried, and evaporated to give a solid which melted at 85.5–86.2°, after one crystallization from ethyl acetate-petroleum ether. One more crystallization gave m.p. 86.5–87.5°, $[\alpha]_D^{23}$ +5.2° (C 5.2, HOAc). (lit.[6] m.p. 87°, $[\alpha]_D^{18}$ +5.3° (±0.2) (C 6.6, HOAc).

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.40; H, 5.70; N, 4.69. Found: C, 68.43; H, 5.67; N, 4.79.

Isolation of sodium complex of benzyloxycarbonyl-L-phenylalanine. The alkaline solution resulting from the Schotten-Baumann acylation of L-phenylalanine with benzyloxycarbonyl chloride was acidified to *p*H 5. The precipitate which formed was removed by filtration, m.p. 132.5–133.5°. This solid was analyzed directly after drying at 120° for two days *in vacuo*.

Anal. Calcd. for $C_{34}H_{33}N_2O_8Na$: C, 65.89; H, 5.36; N, 4.51; Na, 3.70. Found: C, 65.98; H, 5.45; N, 4.62; Na, 2.79.

Preparation of the sodium complex of benzyloxycarbonyl-DL-phenylalanine. A solution of 0.5009 g. (0.00168 mole) of benzyloxycarbonyl-DL-phenylalanine in aqueous ethanol was half-neutralized with 8.4 ml. of 0.100*N* sodium hydroxide. Evaporation of the solvent under reduced pressure and drying in vacuo yielded a crystalline solid which melted at 165–167°. After recrystallization from ethyl acetate the material melted at 168–168.3°. A mixed melting point determination with the original complex (m.p. 168.5–169° isolated previously) melted at 168–168.7°. Also, the infrared spectrum was identical with that obtained from the original complex.

Preparation of other complexes. In a fashion similar to that described above, several other amino acid derivatives were treated with one-half equivalent of standard base and the products isolated by evaporation. The data are summarized in Table I.

TABLE I
1:1 COMPLEXES FORMED BY HALF NEUTRALIZATION[a]

Original Compound	M.P.	Treated with One-half Equiv. of	M.P. of Product
Benzyloxycarbonyl-L-phenylalanine	87°	NaOH	129.5–132°
Benzyloxycarbonyl-DL-phenylalanine	102°	KOH	179.2–180.5°
Benzyloxycarbonyl-DL-phenylalanine	102°	LiOH	Mixture of oil and crystals
Benzyloxycarbonyl-glycyl-L-phenylalanine	122°	NaOH	160–164.8°
Formyl-DL-phenylalanine	167°	NaOH	204–206° dec.

[a] These materials have been shown to contain no water of hydration by Karl-Fischer titration.

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(7) All melting points are uncorrected.

(8) Microanalyses by Schwarzkopf Laboratories, Woodside, N. Y.

(9) M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).

A Synthesis of 2-Amino-6-trifluoromethylpurine

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In the course of metabolite antagonist studies, 2-amino-6-trifluoromethylpurine was required for biological evaluation. Its synthesis in good overall yield was completed in this laboratory prior to a report by Bendich *et al.*[2] describing an alternate procedure without experimental details. Our route is analogous to the method of Gabriel and Colman[3] for the synthesis of 6-methylpurine. 6-Trifluoromethyl-2-thiouracil[4] was converted to 6-trifluoromethyluracil in a manner patterned after the

(1) Smith Kline & French Laboratories Fellow, 1955–1957.

(2) A. A. Bendich, Giner-Sorolla, and J. J. Fox, *Ciba Foundation Symposium on the Chemistry and Biology of Purines*, Little, Brown & Co., Boston, 1957, p. 3.

(3) S. Gabriel and J. Colman, *Ber.*, **34**, 1234 (1901).

(4) W. H. Miller, A. M. Dessert, and G. W. Anderson, *J. Am. Chem. Soc.*, **70**, 300 (1948).

preparation of uracil from thiouracil.[5] This compound was also prepared, in poor yield, from ethyl trifluoroacetoacetate and urea in the presence of sodium ethoxide as reported for similar cases.[6] A nitro group was introduced into the 5-position of 6-trifluoromethyluracil by using a strong nitrating mixture, and the two hydroxyl groups of the nitro compound were replaced by chlorination with phosphorus oxychloride and dimethylaniline. The chlorine atoms were exchanged with amino groups, and the resulting 2,4-diamino-5-nitro-6-trifluoromethylpyrimidine was hydrogenated to 2,4,5-triamino-6-trifluoromethylpyrimidine. The sulfate of this compound underwent purine ring closure when treated with formamide by the general directions of Robins *et al.*[7] 2-Amino-6-trifluoromethylpurine from this sequence was a crystalline amphoteric compound whose infrared spectrum showed pronounced amino (2.84 μ) and imino (2.99 μ) bands. The ultraviolet spectrum was determined in 3*N* hydrochloric acid, where it demonstrated a weak shoulder between 230 and 240 μ, and a maximum at 334 mμ ($\epsilon = 5.05 \times 10^3$); in water to which just sufficient hydrochloric acid was added to accomplish solution (*p*H 2.82), a weak shoulder was observed between 235 and 245 mμ and a maximum at 324 mμ ($\epsilon = 5.88 \times 10^3$).

EXPERIMENTAL

6-Trifluoromethyluracil. Method A. To a solution of 4 g. of sodium ethoxide in 30 ml. of absolute ethanol was added 1.82 g. of urea and 5.5 g. of ethyl trifluoroacetate. The mixture was refluxed for 24 hr., and the solvent was distilled off. The brown residue was dissolved in 15 ml. of water, cooled in an ice bath, and acidified with concentrated hydrochloric acid to produce 1.1 g. (20%) of colorless crystals; m.p. 230–232°. Recrystallization from hot water did not elevate the melting point.

Anal. Calcd. for $C_5H_3F_3N_2O_2$: C, 33.34; H, 1.68. Found: C, 32.70; H, 1.85.

Method B. A mixture of 46 g. of 6-trifluoromethyl-2-thiouracil,[4] 41.4 g. of chloroacetic acid and 500 ml. of water was stirred and refluxed for 4 hr. The resulting pale yellow solution was cooled to room temperature and a colorless crystalline solid precipitated. After addition of 120 ml. of 38% hydrochloric acid the suspension was refluxed and stirred for 6 hr. The solvents were distilled off under reduced pressure and the colorless residue was recrystallized from hot water to yield 38.4 g. (88%) of colorless prisms; m.p. 230–232°. A mixture melting point of this material with a sample obtained by Method A was not depressed. Elementary analysis indicated complete removal of sulfur.

5-Nitro-6-trifluoromethyluracil. A mixture of 30 g. of 6-trifluoromethyluracil, 15 ml. of concentrated sulfuric acid and 60 ml. of fuming nitric acid (d = 1.5) was heated on a steam bath for 1 hr. The yellow solution was transferred to an evaporating dish and heated an additional hour on a steam bath, cooled, and 50 g. of crushed ice was added. The light yellow crystals were recrystallized from a small amount of water to yield 22.2 g. (59%) of almost colorless prisms; m.p. 239–241°. A mixture of this material and 6-trifluoromethyluracil melted at 179–193°. Sodium hydroxide and ferrous hydroxide tests for the nitro group were positive.

Anal. Calcd. for $C_5H_2F_3N_3O_4$: C, 26.68; H, 0.89. Found: C, 26.94; H, 1.20.

2,4-Dichloro-5-nitro-6-trifluoromethylpyrimidine. To 15 g. of 5-nitro-6-trifluoromethyluracil was added 15 ml. of freshly distilled dimethylaniline and 120 ml. of freshly distilled phosphorus oxychloride, while cooling in an ice bath. The dark green solution was refluxed for 2 hr., allowed to stand at room temperature overnight, and concentrated under reduced pressure to one third the original volume. The residual liquid was slowly poured onto 300 g. of stirred crushed ice, the mixture was extracted thoroughly with ether, dried over anhydrous sodium sulfate, and the solvent was distilled off. The resulting black, oily residue was distilled under reduced pressure to yield 9.4 g. (54%) of a light yellow oil; b.p. (0.3 mm.) 48°, which formed a low melting solid when cooled below 0°. A ferrous hydroxide test for the nitro group was positive.

Anal. Calcd. for $C_5Cl_2F_3N_3O_2$: C, 22.92. Found: C, 21.76; 21.70.

2,4-Diamino-5-nitro-6-trifluoromethylpyrimidine. To a saturated solution of ammonia in ethanol (40 ml.), cooled in an ice bath, was added slowly and carefully 8 g. of 2,4-dichloro-5-nitro-6-trifluoromethylpyrimidine. The resulting bright yellow mixture was refluxed for 10 min. and then allowed to stand at room temperature for 24 hr. The precipitated ammonium chloride was filtered and the filtrate was evaporated to dryness on a steam bath. The crystalline residue was suspended in 30 ml. of hot water, cooled, and filtered. Recrystallization from aqueous ethanol afforded 5.4 g. (79%) of bright yellow crystals; m.p. 186–189°. For analysis, a sample was recrystallized from a small amount of ethanol to give bright yellow needles, m.p. 188–190°.

Anal. Calcd. for $C_5H_4F_3N_5O_2$: C, 26.91; H, 1.81. Found: C, 26.62; H, 1.81.

2,4,5-Triamino-6-trifluoromethylpyrimidine. A solution of 4.5 g. of 2,4-diamino-5-nitro-6-trifluoromethylpyrimidine in 100 ml. of absolute ethanol was hydrogenated at 2 atmospheres pressure and room temperature in the presence of 0.2 g. of Adams' catalyst until the hydrogen uptake ceased (20 min.). The catalyst was removed and the brown filtrate was concentrated to dryness under reduced pressure. The residue was recrystallized from about 25 ml. of water, using decolorizing carbon, to afford 3.7 g. (87%) of light tan crystals; m.p. 197–199°.

Anal. Calcd. for $C_5H_6F_3N_5$: C, 31.09; H, 3.13. Found: C, 30.90; H, 3.14.

This material (3.0 g.) was converted to the sulfate by dissolving in 15 ml. of warm 10% sulfuric acid and evaporating the solution to dryness on a steam bath. The light yellow crystalline residue was recrystallized from ethanol-ether, using decolorizing carbon, to give 3.3 g. (88%) of a colorless powder; m.p. 173–175° dec., with preliminary softening at 160°.

Anal. Calcd. for $C_{10}H_{14}N_{10}F_6SO_4$: C, 24.80; H, 2.92. Found: C, 25.05; H, 2.81.

2-Amino-6-trifluoromethylpurine. To 3.0 g. of 2,4,5-triamino-6-trifluoromethylpyrimidine sulfate was added 20 ml. of redistilled formamide. The mixture was heated at 180–190° bath temperature for 20 min., allowed to cool to 30°, diluted with 20 ml. of water, and cooled to 0° for 24 hr. The light tan crystals were filtered, and washed with water, ethanol, and ether. The product (2.0 g., 80%) was precipitated twice with ammonia from hot 10% hydrochloric acid, using decolorizing carbon, to produce colorless crystals; m.p. above 320°.

Anal. Calcd. for $C_6H_4F_3N_5$: C, 35.47; H, 1.99. Found: C, 35.62; H, 2.00.

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