solution,[11] then with water. After drying the oil over sodium sulfate the fraction of b.p. 150–175°/40–50 mm. was collected as a colorless liquid which solidified to 220 g. (83%) of white prisms, m.p. 41°.

*Anal.* Calcd. for $C_{11}H_{16}OSi$: C, 68.72; H, 8.39. Found: C, 68.99; H, 8.27.

This compound was characterized as the semicarbazone, oxime, phenylhydrazone, and 2,4-dinitrophenylhydrazone.

*4-Trimethylsilylacetophenone semicarbazone.* This derivative was formed in the standard manner. Two recrystallizations from isopropyl alcohol yielded colorless needles, m.p. 221°.

*Anal.* Calcd. for $C_{12}H_{19}N_3OSi$: N, 16.85. Found: N, 16.82.

*4-Trimethylsilylacetophenone oxime.* To a solution of hydroxylamine hydrochloride (5 g.) in water (10 ml.) were added I (12.8 g.) and a solution of sodium hydroxide (3 g.) in water (5 ml.). Isopropyl alcohol was cautiously added until, on warming to about 70°, the solution became clear and free from insoluble droplets. The mixture was heated at reflux on the water bath for 4 hr., then poured into water (100 ml.), and allowed to crystallize overnight. The stubby prismatic crystals were filtered, washed with water, and drained, m.p. 90–91°. Yield, 13.7 g. (99%). Two recrystallizations from alcohol raised the m.p. to 92°.

*Anal.* Calcd. for $C_{11}H_{17}NOSi$: N, 6.76. Found: N, 6.74.

*4-Trimethylsilylacetophenone phenylhydrazone and 2,4-dinitrophenylhydrazone.* The phenylhydrazone was prepared by the same procedure as that employed for acetophenone phenylhydrazone.[12] Recrystallization from alcohol yielded very pale yellow needles, m.p. 93°. On standing at room temperature for two to three days the crystals darkened considerably and began to decompose. It is well known that the acetophenone derivative behaves similarly.

The *2,4-dinitrophenylhydrazone*[4] was prepared in the usual manner and melted at 195°.

*Anal.* Calcd. for $C_{17}H_{20}N_4O_4Si$: N, 15.05. Found: N, 14.94.

*Di(4-acetylphenyl)dimethylsilane.* This compound was prepared in a manner similar to that employed for the preparation of I, using the following amounts of reactants: magnesium turnings (60 g., 2.47 g. atoms), ketal (II) (486 g., 2.0 moles), dimethyldichlorosilane (129 g., 1.0 mole). After addition of dilute hydrochloric acid, ether extraction and washing with saturated calcium chloride followed by water, the ether solution was dried over sodium sulfate, then distilled. The colorless liquid (172 g., 58%) of b.p. 287–290°/40 mm. was collected and crystallized in the receiver. Two recrystallizations from alcohol gave white needles, m.p. 130°.

*Anal.* Calcd. for $C_{18}H_{20}O_2Si$: C, 72.95; H, 6.80. Found: C, 72.77; H, 6.58.

*Di(4-acetylphenyl)dimethylsilane disemicarbazone* was prepared in the usual manner. Recrystallization from alcohol gave white needles, m.p. 137°.

*Anal.* Calcd. for $C_{20}H_{26}N_6O_2Si$: N, 20.48. Found: N, 20.37.

*Acknowledgment.* The author thanks Mr. Richard G. Tonkyn for helpful discussions concerning this work. Thanks are also due to Miss Ethel Schiavon and Mr. Joseph Wirth for their experimental assistance.

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(11) A stable emulsion results if water is used as the first wash liquid.

(12) H. Reisenegger, *Ber.*, 16, 662 (1883); R. L. Shriner, W. C. Ashley, and E. Welch, *Org. Syntheses*, Coll. Vol. III, 726, (1955); F. G. Mann and B. C. Saunders, "Practical Organic Chemistry," Longmans, Green and Co., London, 1949, p. 177.

## Alkali Metal Complexes of Phenylalanine Derivatives[1,2]

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*Received June 30, 1958*

During the course of our work on the synthesis of peptides, we noted disagreement in the literature as to the correct melting point of benzyloxycarbonyl-L-phenylalanine. Bergmann[3] and Smith[4] reported 126–128° for the L- and D-isomers respectively but Holley[5] pointed out that this material possessed abnormally high neutralization equivalents. In addition, Holley[5] found that the neutralization equivalent could be lowered considerably by treating the product with dilute hydrochloric acid. Recently, Kenner[6] and coworkers, employing countercurrent distribution, were able to isolate a fraction which had the correct neutralization equivalent and melted at 87°. In this communication we wish to report that the high melting materials previously isolated were complexes of benzyloxycarbonyl-L-phenylalanine with its sodium salt. Conclusive evidence for the nature of these complexes was initially obtained in our laboratories using the DL-isomer.

When we prepared benzyloxycarbonyl-DL-phenylalanine, we observed the appearance of a side product which melted at 168°, much higher than the recorded 103° of the desired product. Elemental analyses, molecular weight, and infrared spectra indicated that the side product was a 1:1 complex of benzyloxycarbonyl-DL-phenylalanine with its sodium salt. This substance was subsequently shown to be identical with that obtained by half-neutralizing a sample of the pure acid with standard sodium hydroxide.

In the case of the corresponding L-isomer the product prepared in the usual way consists of varying quantities of the free acid and its sodium salt as evidenced from the neutralization equivalents reported.[5,6] These crude products can be converted to pure benzyloxycarbonyl-L-phenylalanine melting at 87° by extended treatment with hydrochloric acid. It is possible, however, to isolate a substance corresponding almost exactly to a 1:1 complex by acidifying the Schotten-Baumann reaction mixture to *p*H 5. Further acidification

(1) Presented before the Organic Section of the American Chemical Society at the 133rd meeting, San Francisco, Calif., April 1958.

(2) This research was supported by a grant from the National Science Foundation.

(3) M. Bergmann, L. Zervas, H. Rinke, and H. Schleich, *Z. physiol. chem.*, 224, 33 (1934).

(4) C. S. Smith and A. E. Brown, *J. Am. Chem. Soc.*, 63, 2605 (1941).

(5) R. W. Holley and A. D. Holley, *J. Am. Chem. Soc.*, 74, 3069 (1952).

(6) D. W. Clayton, J. A. Farrington, G. W. Kenner, and J. M. Turner, *J. Chem. Soc.*, 1398 (1957).

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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*Received July 3, 1958*

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.

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