[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

Fluorinated Aromatic Amino Acids.[1,2] II. 2- and 3-Trifluoromethyltyrosines. Hydrolytic Stability of the Trifluoromethyl Group on the Aromatic Nucleus

ROBERT FILLER AND HERMAN NOVAR

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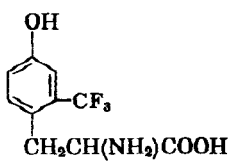
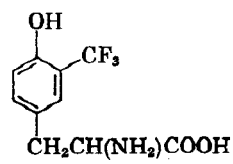
2-Trifluoromethyl-DL-tyrosine (I) was prepared in 17% yield by the reaction of 2-trifluoromethyl-4-hydroxy benzenediazonium chloride with acrylic acid (Meerwein reaction), followed by ammonolysis. Attempts to prepare I *via* the azlactone route failed. 3-Trifluoromethyl-DL-tyrosine (II) could not be prepared by either of these pathways, although 3-trifluoromethyl-4-methoxy-DL-phenylalanine was obtained in impure form by the Meerwein route. The critical factor in the failure to synthesize II was the hydrolytic instability (in both acid and alkaline medium) of the trifluoromethyl group *ortho* to a hydroxyl group.

In an earlier paper,[3] the syntheses of the three isomeric ring-substituted trifluoromethylphenylalanines were described as part of a study of the effects of trifluoromethyl substitution on the physical properties and physiological activity of aromatic amino acids. In the present paper we report our studies on the preparation of the structurally related trifluoromethyltyrosines I and II.



I



II

Our approach to the syntheses of I and II centered on reactions of a common intermediate, 2-chloro-5-nitrobenzotrifluoride (III), which was prepared in 87% yield by nitration of *o*-chlorobenzotrifluoride.[4] In theory, both I and II could be obtained if either the nitro or chloro group were converted into hydroxyl and the other group *para* to it transformed into the amino acid side chain.

Although we are not aware of examples of Grignard reagents prepared from nitro-substituted aryl halides,[5] we attempted, unsuccessfully, the preparation of Grignard reagents from III or its 2-bromo analog[6] both in ether and tetrahydrofuran. III was reduced to 2-chloro-5-aminobenzotrifluoride, but this compound also failed to form a Grignard reagent. The aldehyde-azlactone pathway to the amino acid I was therefore abandoned.

We have previously demonstrated[7] the usefulness of the Meerwein reaction[8] for the preparation of aromatic amino acids. Interaction of aryl diazonium chlorides and acrylic acid in buffered, aqueous acetone containing cupric chloride gave α-chloro-β-arylpropionic acids. Ammonolysis of the chloro acids in concentrated aqueous ammonia gave the corresponding amino acids. In this manner, 3-trifluoromethyl-4-aminophenol (IV), obtained by catalytic reduction of 3-trifluoromethyl-4-nitrophenol,[9] was converted into DL-2-trifluoromethyltyrosine (I) in 17% yield.

This new amino acid gave a positive ninhydrin reaction and a positive Millon's test, although the rate of development of the characteristic red color was considerably slower than for tyrosine itself. This was probably due to the reduced rate of nitration of the trifluoromethyl analog relative to tyrosine.

DL-Tyrosine exhibited ultraviolet absorption at 276 mμ and 226 mμ in 95% ethanol. These maxima shifted to 298 mμ and 246 mμ on addition of alkali (*p*H 12) due to formation of phenolate ion.[10] 2-Trifluoromethyltyrosine behaved similarly with the free phenol exhibiting maxima at 284 mμ (ϵ 3260) and 229 mμ (ϵ 10,200), whereas at *p*H 11.0–11.3, shifts to 305 mμ (ϵ 12,900) and 251 mμ (ϵ 28,800) were observed.

For the synthesis of II by either the azlactone or Meerwein routes, we considered it desirable to prepare 2-trifluoromethyl-4-nitrophenol, which could then be converted to either the 4-bromo or the 4-amino analog, as required. When III was treated with aqueous potassium hydroxide under reflux conditions, the only product isolated was 5-nitrosalicylic acid, V.

(1) This work was supported by a grant (CY-4532) from the National Cancer Institute, National Institutes of Health, USPHS.

(2) Abstracted from the Ph.D. thesis of Herman Novar, June 1961.

(3) R. Filler and H. Novar, *J. Org. Chem.*, 25, 733 (1960).

(4) We wish to thank Hooker Electrochemical Co. for a generous supply of *o*-chlorobenzotrifluoride.

(5) Usually such Grignard reagents, if prepared, react rapidly with the starting material to give products of reduction of the nitro group. *Cf.* M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, New York, 1954, pp. 1237–1242.

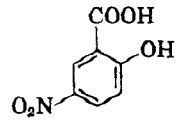
(6) Compound III reacted with liquid ammonia under pressure to give the 2-amino compound from which 2-bromo-5-nitrobenzotrifluoride was obtained by the Sandmeyer reaction.

(7) R. Filler and H. Novar, *Chem. & Ind.*, 468 (1960).

(8) H. Meerwein, E. Büchner, and K. van Emster, *J. prakt. Chem.*, 152, 237 (1939); C. F. Koelsch, *J. Am. Chem. Soc.*, 65, 57 (1943).

(9) We thank the Maumee Chemical Co., Toledo, Ohio, for a sample of this material, marketed as 2-nitro-5-hydroxybenzotrifluoride.

(10) See, *e.g.*, I. W. Sizer and A. C. Peacock, *J. Biol. Chem.*, 171, 767 (1947).



V

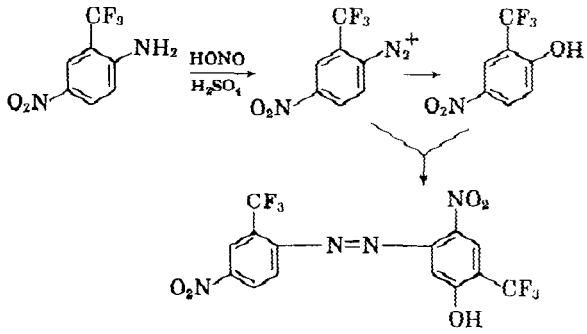
Other methods of alkaline hydrolysis of III led to the same product or to recovery of starting material. *In no case did we observe a product in which the hydroxyl had replaced the chloro group with the trifluoromethyl group left intact.* These observations support the postulate previously proposed[11] that reactions used to prepare compounds containing an —OH group *ortho* to —CF_3 and which involve strongly alkaline conditions, lead to rapid hydrolysis of the trifluoromethyl group to carboxylate ion.[12]

However, III reacted with sodium methoxide in anhydrous methanol or potassium hydroxide in aqueous methanol to give 2-methoxy-5-nitrobenzotrifluoride (VI) in 85–93% yields. In these cases, the trifluoromethyl group was not attacked, again demonstrating the importance of the phenoxide ion in facilitating the alkaline hydrolysis of the trifluoromethyl group. The demethylation of VI was attempted using glacial acetic acid and 48% hydrobromic acid under reflux conditions. The course of the reaction was followed by removing samples periodically and testing for the presence of a phenol with ferric chloride. No reaction occurred until the fourth day, at which time a positive ferric chloride test was observed and 5-nitrosalicylic acid was isolated. Thus, under *acid* conditions, the trifluoromethyl group attached to the aromatic nucleus is often very vulnerable to hydrolysis, although the nature and position of other nuclear substituents relative to trifluoromethyl markedly influence this susceptibility to hydrolytic attack.[11] It appears that the trifluoromethyl group in VI is stable to the acid mixture until demethylation occurs, at which time participation of the ortho —OH group ("no bond" resonance and hydrogen bonding) assists in weakening the C—F bond, leading to destruction of the trifluoromethyl group.

Compound VI was reduced to 2-methoxy-5-aminobenzotrifluoride, isolated as its hydrochloride (VII). All attempts to demethylate this amino ether using hydrobromic acid, hydriodic acid or mixtures of the two, resulted either in recovery of starting material or evidence of decomposition of the trifluoromethyl group. Compound VII was converted to 2-methoxy-5-bromobenzotrifluoride (VIII) *via* the Sandmeyer reaction. The latter compound failed to form a Grignard reagent in ether, and, although a reaction in tetrahydrofuran was observed, no aldehyde could be isolated on treatment with *N*-methylformanilide. Attempted demethylation of VIII also failed. As in the case of I, the aldehyde-azlactone route was abandoned in favor of the Meerwein path.

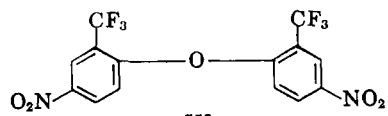
Compound VII was diazotized, treated with acrylic acid, and aminated, according to the procedure described earlier. The impure 3-trifluoromethyl-4-methoxyphenylalanine gave a strong positive ninhydrin reaction, but all attempts to purify this material, including ion-exchange chromatography, vacuum sublimation, and more conventional methods, were unsuccessful. We were also unable to demethylate this substance to form II.

We examined several other approaches to compounds possessing an —OH group *ortho* to —CF_3, including. 1) Diazotization of 2-amino-5-nitrobenzotrifluoride and the decomposition of the diazonium salt. No simple phenolic product could be detected, but a bright orange solid was isolated which appeared to be an azo dye. We suggest the following series of reactions as a plausible interpretation of this observation:



Hauptschein[13] obtained similar results by treating the diazotization product of anthranilic acid with *m*-trifluoromethylphenol.

2) In an attempt to form the benzyl ether of 2-trifluoromethyl-4-nitrophenol, which could then be converted to the phenol by hydrogenolysis, III was treated with sodium benzylate. Instead of the ether, a yellow crystalline product was isolated which showed no evidence of hydrolysis of the trifluoromethyl group and whose elemental analysis and molecular weight strongly suggested the structure IX, 2,2′-bistrifluoromethyl-4,4′-dinitrophenyl ether.



IX

(11) R. Filler and H. Novar, *Chem. & Ind.*, 1273 (1960).

(12) This conclusion is consistent with earlier observations that the trifluoromethyl group is hydrolyzed by strong base with extraordinary facility if hydroxyl or amino groups are located *ortho* or *para* to the trifluoromethyl group. See R. G. Jones, *J. Am. Chem. Soc.*, 69, 2346 (1947); J. Bornstein, S. A. Leone, W. F. Sullivan, and O. F. Bennett, *J. Am. Chem. Soc.*, 79, 1745 (1957). This behavior has been attributed to "no bond" resonance: (J. D. Roberts, R. L. Webb, and E. A. McElhill, *J. Am. Chem. Soc.*, 72, 408 (1950)).

(13) M. Hauptschein, A. J. Saggiomo, and C. S. Stokes, *J. Am. Chem. Soc.*, 77, 2284 (1955).

3) *o*-Aminobenzotrifluoride[14] was converted to *o*-trifluoromethylphenol *via* the diazonium salt. The amount of phenol obtained was insufficient for nitration and subsequent reactions. It is probable that under usual nitration conditions the trifluoromethyl group would be hydrolyzed.

EXPERIMENTAL[15]

2-Chloro-5-nitrobenzotrifluoride. *o*-Chlorobenzotrifluoride (100 g.), 150 cc. of sulfuric acid and 100 cc. of nitric acid were stirred for 18 hr. and a strongly exothermic reaction occurred. The organic layer was washed with water, neutralized with solid sodium bicarbonate and washed again with water. Distillation gave 109 g. (87%) of 2-chloro-5-nitrobenzotrifluoride, b.p. 100° (8 mm.); n_D^{30} 1.5031, (lit.[16] b.p. 108° (10 mm.); n_D^{30} 1.5043).

2-Chloro-5-aminobenzotrifluoride. 2-Chloro-5-nitrobenzotrifluoride (50 g.), dissolved in 150 cc. of 95% ethanol, was reduced by hydrogen using 0.1 g. of platinum oxide as catalyst. The mixture was shaken for 3 hr. at room temperature. The ethanol was removed and the residue distilled to give 33 g. (76%) of 2-chloro-5-aminobenzotrifluoride, b.p. 106° (5 mm.); $n_D^{24.5}$ 1.5118. The colorless distillate quickly turned amber. This material was compared with an authentic sample, b.p. 107° (7 mm.); $n_D^{24.5}$ 1.5132.

Hydrolysis of 2-chloro-5-nitrobenzotrifluoride. In a typical conversion, 10 g. of the halo compound was refluxed with 6*N* aqueous potassium hydroxide for 5 hr. The dark solution was filtered and the filtrate acidified with dilute aqueous sulfuric acid. The resulting precipitate gave a positive ferric chloride test and after recrystallization from hot water, was shown to be 5-nitrosalicylic acid, m.p. 225–228°. When the conditions of this reaction were varied, no reaction occurred or the same product was obtained. 2-Hydroxy-5-nitrobenzotrifluoride was never detected.

2-Methoxy-5-nitrobenzotrifluoride. Method A. 2-Chloro-5-nitrobenzotrifluoride (45.2 g., 0.2 mole) was added dropwise into a 500-cc. three-necked flask equipped with stirrer, condenser, and an addition funnel and which contained a mixture of sodium methoxide in methanol, prepared by reaction of 4.6 g. of sodium with 100 cc. of anhydrous methanol. An amber precipitate formed as the halo compound was added and the temperature of the mixture rose until the methanol began to reflux. After addition was complete, stirring was continued overnight at room temperature and the mixture acidified with 6*N* hydrochloric acid and extracted with 200 cc. of ether. The ether layer was separated, dried over anhydrous magnesium sulfate, and the ether distilled. The residue was recrystallized from 95% ethanol to yield 38 g. (86%) of 2-methoxy-5-nitrobenzotrifluoride, m.p. 79–79.5°.

Anal. Calcd. for $C_8H_6NO_3F_3$: C, 43.44; H, 2.74. Found: C, 43.33; H, 2.71.

Method B: 2-Chloro-5-nitrobenzotrifluoride (80 g.) was added dropwise with stirring to a solution of 50 g. of potassium hydroxide in 400 cc. of methanol. A deep red color developed and faded, a precipitate formed, and the temperature of the system rose slowly as the reaction proceeded. The mixture was stirred for 15 min. at room temperature, 6*N* hydrochloric acid was added, and the mixture turned white. After cooling, 250 cc. of water were added to give 75 g. (93%) of 2-methoxy-5-nitrobenzotrifluoride of sufficient purity to be used without further treatment.

Demethylation and hydrolysis of 2-methoxy-5-nitrobenzotrifluoride. 2-Methoxy-5-nitrobenzotrifluoride was dissolved in glacial acetic acid and enough 48% hydrobromic acid was added just to separate the system into two phases. The mixture was heated under reflux for 4 days and samples of the solution were tested for the phenol periodically both by ferric chloride solution and isolation of any product. The sample was extracted with ether, the organic layer shaken with dilute aqueous sodium hydroxide, and the alkaline solution acidified, extracted with ether, and the ether evaporated. None of the solutions isolated prior to the fourth day gave a positive ferric chloride test or yielded any residue during attempted isolation. After 4 days, the solution gave a positive ferric chloride test. The remaining solution was worked up as described to give a white solid which crystallized from acetone–benzene–petroleum ether 60–80°. This solid began to sublime at 197° and melted at 230°. The etching of the glass was evidence of hydrolysis of the trifluoromethyl group. A mixed melting point with an authentic sample of 5-nitrosalicylic acid showed no depression.

2-Methoxy-5-aminobenzotrifluoride. 2-Methoxy-5-nitrobenzotrifluoride (7.0 g.), dissolved in 100 cc. of 95% ethanol, was reduced by hydrogen using 0.5 g. 5% palladium on charcoal catalyst. The solvent was removed leaving a dark oil. This material crystallized from boiling petroleum ether to give 4.9 g. (82%) of 2-methoxy-5-aminobenzotrifluoride, m.p. 59–60°. Because of the low melting point of the amine, the compound was generally isolated as the hydrochloride.

Anal. Calcd. for $C_8H_8NOF_3$: C, 50.26; H, 4.22. Found: C, 50.38; H, 4.27.

2-Methoxy-5-bromobenzotrifluoride. 2-Methoxy-5-aminobenzotrifluoride hydrochloride was mixed with excess 48% hydrobromic acid and treated with aqueous sodium nitrite at 0°. The mixture was poured quickly into a hot mixture of cuprous bromide–hydrobromic acid in a flask arranged for distillation and the resulting mixture was distilled until only one phase condensed into the receiver. The distillate was extracted with ether, the ether extract dried over anhydrous magnesium sulfate and the ether evaporated. Distillation gave a colorless liquid, b.p. 120° (30 mm.); n_D^{42} 1.4907.

Anal. Calcd. for $C_8H_6NBrF_3$: C, 37.53; H, 2.68. Found: C, 37.67; H, 2.37.

2-Amino-5-nitrobenzotrifluoride. 2-Chloro-5-nitrobenzotrifluoride (75 g.) was placed in a bomb and cooled in a Dry Ice–acetone bath for 30 min. Seventy cubic centimeters of liquid ammonia was added, the bomb quickly sealed and shaken for 18 hr. at 100°. After cooling to room temperature, the bomb was again placed in Dry Ice–acetone and, after 30 min., carefully opened and again allowed to warm to room temperature to permit excess ammonia to escape. A yellow solid was removed and any residue dissolved in boiling ethanol. The solid crystallized from benzene–petroleum ether to give 62 g. (97%) of yellow 2-amino-5-nitrobenzotrifluoride, m.p. 91.5–93°.

Anal. Calcd. for $C_7H_5N_2O_2F_3$: C, 40.62; H, 2.84. Found: C, 40.78; H, 2.44.

2-Bromo-5-nitrobenzotrifluoride. 2-Amino-5-nitrobenzotrifluoride was converted to 2-bromo-5-nitrobenzotrifluoride *via* the Sandmeyer reaction in a manner similar to that used in the preparation of 2-methoxy-5-bromobenzotrifluoride (*vide supra*). Distillation of the resulting oil gave yellow 2-bromo-5-nitrobenzotrifluoride, b.p. 125–130° (12 mm.); n_D^{38} 1.5263.

Anal. Calcd. for $C_7H_3NO_2BrF_3$: C, 31.13; H, 1.12. Found: C, 31.96; H, 1.45.

Attempted formation of 2-hydroxy-5-nitrobenzotrifluoride. 2-Amino-5-nitrobenzotrifluoride (21 g., 0.1 mole), mixed with 50 cc. of concd. sulfuric acid and 100 cc. of water, was cooled to −5°. A cold solution of sodium nitrite (7.0 g.), dissolved in 20 cc. of water, was added dropwise with stirring. The mixture was allowed to warm to room temperature and was stirred overnight. There was no evidence of nitrogen evolution. The aqueous mixture was extracted with 200 cc. of ether and the ether evaporated to yield a bright orange solid which crystallized from acetone-water, m.p. 172.5–174°.

2,2'-Bistrifluoromethyl-4,4'-dinitrodiphenyl ether. Ten grams of sodium was dissolved in 200 cc. of benzyl alcohol

(14) Supplied by Pierce Chemical Co., Rockford, Ill.

(15) Melting points are corrected.

(16) I. G. Farbenind., A.-G., French Pat. 745,293 (May 8, 1933); *Chem. Abstr.*, 27, 4413 (1933).

and 2-chloro-5-nitrobenzotrifluoride (42 g., 0.186 mole) was added dropwise with stirring. Stirring was continued for an hour at room temperature and the alkaline mixture acidified with 6*N* hydrochloric acid to give a yellow solid. The solid was dissolved in 150 cc. of ether, the ether solution extracted with 100 cc. of 5% aqueous sodium hydroxide, then with 100 cc. of water, and both aqueous extracts were discarded. On evaporation of the ether, a yellow material precipitated. The solid crystallized from hot methanol to yield 33 g. (90%) of a substance believed to be 2,2'-bistrifluoromethyl-4,4'-dinitrodiphenyl ether, m.p. 141–141.5°. The expected product, the benzyl ether of 2-hydroxy-5-nitrobenzotrifluoride, was not detected.

Anal. Calcd. for $C_{14}H_6N_2O_5F_6$: C, 42.44; H, 1.53; N, 7.07; mol. wt., 396. Found: C, 42.01; H, 1.64; N, 7.75; mol. wt. (Rast), 410.

2-Amino-5-hydroxybenzotrifluoride. 2-Nitro-5-hydroxybenzotrifluoride[17] (40 g.), dissolved in 100 cc. of 95% ethanol, was reduced by hydrogen using 0.5 g. of 5% palladium on charcoal. The mixture was shaken for 3 hr. at room temperature. The solvent was removed leaving a residue which was recrystallized from 95% ethanol to yield 29.5 g. (86%) of 2-amino-5-hydroxybenzotrifluoride, m.p. 154.5–155.5°.

Anal. Calcd. for $C_7H_6NOF_3$: C, 47.46; H, 3.42. Found: C, 47.41; H, 3.64.

Meerwein condensation pathway for amino acids. Sodium acetate (8.5 g.), 3.0 g. of cupric chloride, 7.2 g. of acrylic acid, and 75 cc. of acetone were placed in a 500-cc. round bottomed flask containing a magnetic stirring bar. The flask was partially immersed in a Dry Ice–acetone bath and the mixture was stirred. Twenty cubic centimeters of concd. hydrochloric acid and 10 cc. of water were added to 17.7 g. (0.1 mole) of 2-amino-5-hydroxybenzotrifluoride in a beaker which was also partially immersed in a Dry Ice-acetone bath. A cold solution of 7.0 g. of sodium nitrite in 20 cc. of water was added dropwise while the mixture was stirred, the temperature being kept below 0° during the addition. The diazotized mixture was quickly added to the contents of the flask and the system connected to a mercury-bubble counter. The mixture turned green during the addition. The Dry Ice–acetone bath was removed, the system allowed to warm to room temperature and the mixture stirred for 4 hr. during which time nitrogen was evolved. Generally, bubbling ceased within 2 hr. after the bath had been removed. The contents of the flask were shaken with 150 cc. each of ether and water, the aqueous layer discarded, and 150 cc. of 10% aqueous sodium hydroxide added to the ether solution. The ether extract was discarded, the alkaline solution acidified with 6*N* hydrochloric acid and 200 cc. of ether added to the aqueous mixture. The aqueous layer was separated and the ether was evaporated by air blowing. This was continued until the odor of acrylic acid was no longer evident. The residue was dissolved in 300 cc. of concd. aqueous ammonium hydroxide and the solution placed in a 500-cc. round bottomed flask, which was stoppered. The flask and contents were shaken occasionally over a 4-day period. The contents of the flask were poured into an Erlenmeyer flask and heated on a steam bath while air was blown over the solution until the odor of ammonia could no longer be detected. The mixture was concentrated to 50 cc., powdered charcoal added and the mixture filtered. A double volume of 95% ethanol was added and the solution placed in a refrigerator. 2-Trifluoromethyltyrosine precipitated within 24 hr. After washing with cold absolute ethanol and drying, there was obtained 4.25 g. (17%) of this amino acid, m.p. 212–225° dec.; positive ninhydrin and Millon tests.

Anal. Calcd. for $C_{10}H_{10}NO_3F_3$: C, 48.20; H, 4.05; N, 5.62. Found: C, 48.36; H, 4.54; N, 5.51.

Ultraviolet Spectra. The ultraviolet spectra were obtained on a Beckman DK-2 spectrophotometer.

(17) Supplied by Maumee Chemical Co., Toledo, Ohio.

CHICAGO 16, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, THE HEBREW UNIVERSITY]

Synthesis of Peptides and of Some Polydipeptides of Homoserine by an Aminolactone Method[1]

T. SHERADSKY,[2] Y. KNOBLER, AND MAX FRANKEL

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The use of α-amino-γ-butyrolactone and its derivatives for the synthesis of homoseryl and of *N*-homoserine peptides was investigated. Mixed homoseryl and *N*-homoserine peptides, peptidolactones and unsymmetrically substituted diketopiperazines of homoserine, as well as polymers of mixed *N*-homoserine dipeptides were synthesized.

Homoserine (α-amino-γ-hydroxybutyric acid), a precursor of methionine and of threonine,[3] was found as a bacterial degradation product of canavanine.[4] Virtanen and co-workers isolated homoserine from germinating pea seeds[5] and showed that in certain plants it occurs in peptide bound form.[6]

Various methods were developed for the synthesis of homoserine, of its derivatives as well as for conversion routes to other amino acids,[7–11] but no method was reported for the synthesis of homoserine

(1) Presented in part before the XXVIth Scientific Meeting of the Israel Chemical Society, Jerusalem, April 1960, *cf.* M. Frankel, Y. Knobler, and T. Sheradsky, *Bull. Research Council Israel*, **9A**, 59 (1960).

(2) Part of a Ph.D. Thesis to be submitted to the Hebrew University.

(3) H. J. Teas, N. H. Horowitz, and M. Fling, *J. Biol. Chem.*, **172**, 651 (1948); M. Fling and N. H. Horowitz, *J. Biol. Chem.*, **190**, 277 (1951).

(4) H. Kihara, J. M. Prescott, and E. E. Snell, *J. Biol. Chem.*, **217**, 497 (1955).

(5) A. I. Virtanen, A. M. Berg, and S. Kari, *Acta Chem. Scand.*, **7**, 1423 (1953).

(6) A. I. Virtanen and J. K. Miettinen, *Biochem. et Biophys. Acta*, **12**, 181 (1953); A. I. Virtanen, *Acta Chem. Scand.*, **11**, 747 (1957).

(7) E. Fischer and H. Blumenthal, *Ber.*, **40**, 106 (1907).

(8) J. E. Livak, E. C. Britton, J. C. Vander Weele, and M. F. Murray, *J. Am. Chem. Soc.*, **67**, 2218 (1945).

(9) Y. Knobler and M. Frankel, *J. Chem. Soc.*, 1629 (1953).

(10) M. Frankel and Y. Knobler, *J. Am. Chem. Soc.*, **80**, 3147 (1958); Y. Knobler, S. Livergand, and M. Frankel, *J. Org. Chem.*, **27**, 1794 (1959).