

from benzyl fluoride. Attempts to prepare it under vigorous conditions led to the formation of dibenzyl.
ITHACA, NEW YORK

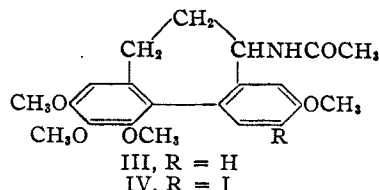
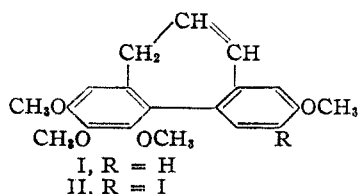
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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

Studies on the Structure of Colchicine.¹ Syntheses in the Biphenyl SeriesBY H. RICHARD FRANK,^{2a} PAUL E. FANTA^{2b} AND D. STANLEY TARBELL

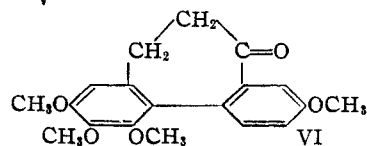
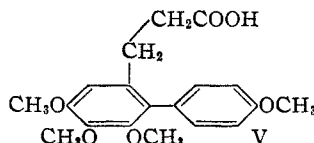
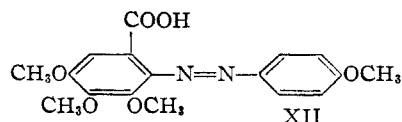
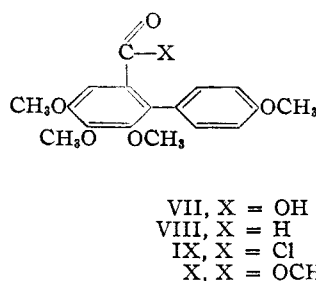
Degradation studies on deaminocolchicol methyl ether³ I and its iodine derivative¹ II have provided evidence for the presence of the central seven-membered ring. Assuming that no rear-

the synthesis of the biphenylpropionic acid V and its ring closure to the ketone VI, which could be converted by obvious methods to compounds I and III.



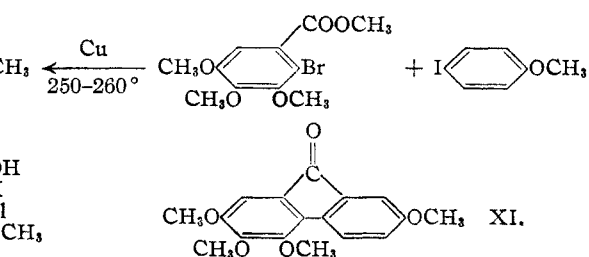
angement of the carbon skeleton occurred during the formation of I or II from N-acetyl-(iodo)-colchicol methyl ether the latter compounds must have structures III and IV. It is obviously necessary, in order to establish the constitution of colchicine, to provide synthetic evidence for structures I-IV. Furthermore, the importance which colchicine and its derivatives have assumed in research on the cancer problem as a result of their antimitotic properties makes it highly desirable to explore possible methods of synthesizing compounds of this type.⁴

Our work was designed to lead to structures I and III through

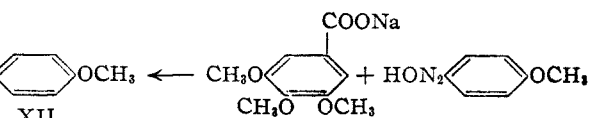


The biphenyl aldehyde VIII seemed to offer a feasible approach to the acid V, since the propionic acid side chain could be readily built up from the aldehyde by condensation with malonic acid followed by decarboxylation and reduction.

The acid VII was therefore prepared in 25-35%



yield by the crossed Ullmann⁵ reaction from *p*-iodoanisole and methyl 2-bromo-3,4,5-trimethoxybenzoate.



oxybenzoate. The Ullmann synthesis using the iodo ester, methyl 2-iodo-3,4,5-trimethoxybenzoate and iodoanisole, yielded the two symmetrical products to the exclusion of the desired unsymmetrical compound VII.

Some preliminary experiments on the preparation of the acid VII by the Gomberg reaction from diazotized *p*-anisidine and sodium 3,4,5-trimethoxybenzoate.

The Ullmann synthesis using the iodo ester, methyl 2-iodo-3,4,5-trimethoxybenzoate and iodoanisole, yielded the two symmetrical products to the exclusion of the desired unsymmetrical compound VII.

(1) In memory of H. Richard Frank, died March 21, 1948; for the preceding paper see Tarbell, Frank and Fanta, *THIS JOURNAL*, **68**, 502 (1946).

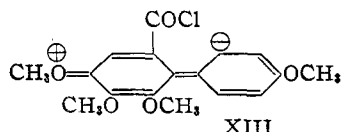
(2) (a) Abbott Laboratories Fellow, 1946-1947. (b) Present address, Department of Chemistry, Harvard University, Cambridge, Massachusetts.

(3) (a) Buchanan, Cook and Loudon, *J. Chem. Soc.*, 325 (1944); (b) Barton, Cook and Loudon, *ibid.*, 176 (1945).

(4) For a discussion of colchicine and other compounds as chemotherapeutic agents for cancer, see Greenstein, "The Biochemistry of Cancer," Academic Press, New York, N. Y., 1947, pp. 170-172.

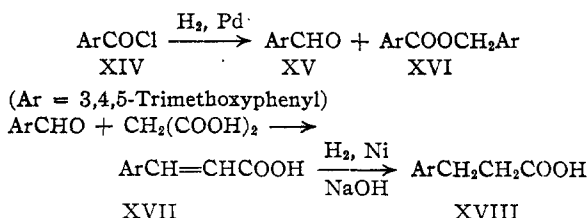
oxybenzoate were unsuccessful, the product being the azo compound XII. The same product was obtained by the action of N-nitroso-N-acetyl-*p*-anisidine on ethyl trimethoxybenzoate, followed by hydrolysis.⁶

When the acid VII was converted to the acid chloride IX even under mild conditions, the latter lost hydrogen chloride spontaneously to form the orange-red 2,3,4,7-tetramethoxyfluorenone XI.⁷



The ester of VII failed to form a hydrazide,⁸ yielding instead what may have been the bis-hydrazide.

In a more successful approach to the synthesis of V, β -(3,4,5-trimethoxyphenyl)-propionic acid was prepared by the previously reported method,⁹ with modifications, according to the scheme



In agreement with previous reports,¹⁰ it was found that the Rosenmund reduction of 3,4,5-trimethoxybenzoyl chloride gave variable yields; a by-product, which in some runs was the main product, was shown to be the ester XVI, by hydrolysis to the expected compounds. This product has been observed by previous workers¹¹ but was not

(6) These results were not entirely unexpected, since Grieve and Hey, *J. Chem. Soc.*, 108 (1938), found that diazotized aniline did not yield a biphenylcarboxylic acid with sodium benzoate. The diazonium compound has two possible modes of reaction, one as the ion ArN_2^+ , to give an azo compound, and the other as the radical Ar \cdot to form a biaryl. It is known (Grieve and Hey, *J. Chem. Soc.*, 1797 (1934)) that the radical reaction goes more slowly with toluene than with nitrobenzene, and hence seems to be retarded by electron-donating groups. The work of Fieser, Clapp and Daudt, *THIS JOURNAL*, 64, 2052 (1942), shows that the methylation of aromatic systems by methyl radicals from lead tetraacetate goes more readily on polynitrated benzenes than on benzene or nitrobenzene. The three methoxyl groups in trimethoxybenzoic acid, being electron-donating groups, inhibit the attack on the ring by a free radical, and promote the attack by the electrophilic diazonium ion.

(7) This fact, while unfavorable for the immediate synthesis of the aldehyde, was nevertheless encouraging evidence for the feasibility of the general synthesis, since it implied that the *m*-methoxyl group in the acid V would not be an insuperable obstacle to cyclization in the desired manner. Recent observations of Johnson and Shelberg, *THIS JOURNAL*, 67, 1853 (1945), indicate that cyclization *meta* to a methoxyl group is not as difficult as had previously been supposed. The extremely facile cyclization of IX is doubtless due to the high electron density in the 2'-position, caused by contributions from resonance forms such as XIII.

(8) This was desired in order to investigate the McFadyen-Stevens method of obtaining aldehydes (*J. Chem. Soc.*, 584 (1936)).

(9) Slotta and Heller, *Ber.*, 63, 3029 (1930).

(10) Cook and Graham, *J. Chem. Soc.*, 322 (1944).

(11) (a) Späth, *Monatsh.*, 40, 141 (1919); (b) Mauthner, *J. prakt. Chem.*, 129, 283 (1931).

identified. Reduction of the cinnamic acid XVII by sodium amalgam⁹ gave a product which was difficult to purify, but the Raney nickel and hydrogen reduction of the sodium salt in aqueous solution¹² gave a practically quantitative yield of the pure hydrocinnamic acid XVIII.

The trimethoxyphenylpropionic acid XVIII was next iodinated, best with iodine monochloride, to yield β -(2-iodo-3,4,5-trimethoxyphenyl)-propionic acid XIX which was esterified with diazomethane to the ester XX. The iodo ester was then coupled with *p*-iodoanisole (in excess) at 250° with copper powder, and the unsymmetrical acid V was isolated in 55% yield.

In order to prevent ring-closure of V from forming the hydrindone XXVII, the free position in the trimethoxylated ring was blocked by bromination, yielding β -2-(3-bromo-4,5,6,4'-tetramethoxybiphenyl)-propionic acid XXI.

The structure of XXI was proved by brominating the trimethoxyphenylpropionic acid XVIII, to yield the monobromo derivative XXIII, which was iodinated by iodine monochloride to the bromiodo compound XXIV. The ester XXV, on coupling with *p*-iodoanisole under the usual conditions, gave a small amount of the same bromo acid which had been obtained previously by direct bromination of the biphenyl acid V.

The problem of cyclizing the acid XXI to the desired ketone XXVI proved very troublesome. The acid was entirely unaffected by anhydrous hydrogen fluoride at room temperature,¹³ and it seemed to be sulfonated to give water-soluble products when treated with sulfuric acid. Treatment of the acid chloride of XXI with phosphorus oxychloride in benzene or toluene gave a small amount of neutral material which proved to be the methyl ester XXII of the acid, apparently formed by intermolecular demethylation. The acid chloride of XXI when treated with stannic chloride in benzene gave no crystalline product.

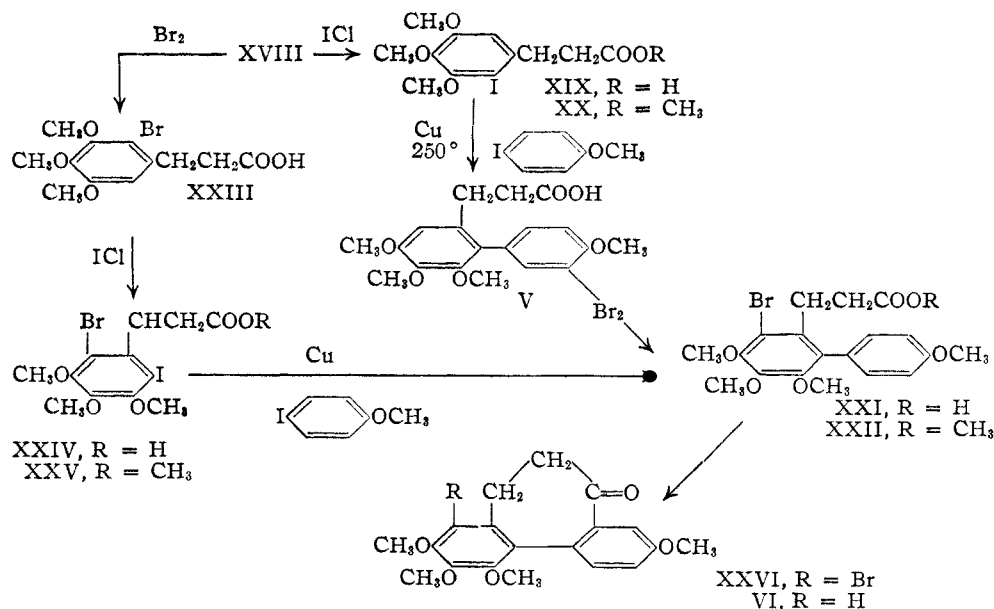
Treatment of the acid chloride with aluminum chloride in tetrachloroethane gave variable results; in one case an impure carbonyl compound was obtained, which from the percentage composition of its oxime and semicarbazone, seemed to be nearly bromine free, and hence might be the desired ketone VI. Structure XXVII was considered as a possible one for this ketonic product, which could be formed from the bromo acid chloride by removal of the bromine¹⁴ followed by ring-closure. The ketone XXVII was actually prepared by cyclization of the unbrominated acid V, and it had quite different properties from the product obtained by the cyclization of the bromo acid XXI.

Although the product from the bromo acid thus appeared to have the desired structure, the poor

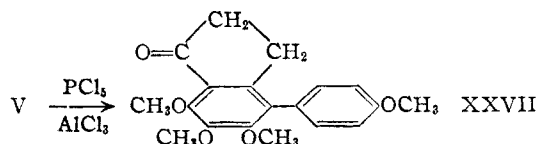
(12) Koelsch and Boekelheide, *THIS JOURNAL*, 66, 414 (1944).

(13) Cf. Johnson and Shelberg, ref. 7.

(14) Halogen migration in aromatic compounds under the influence of acidic catalysts is discussed by Meerwein, Hofmann and Schill, *J. prakt. Chem.*, 154, 266 (1940).

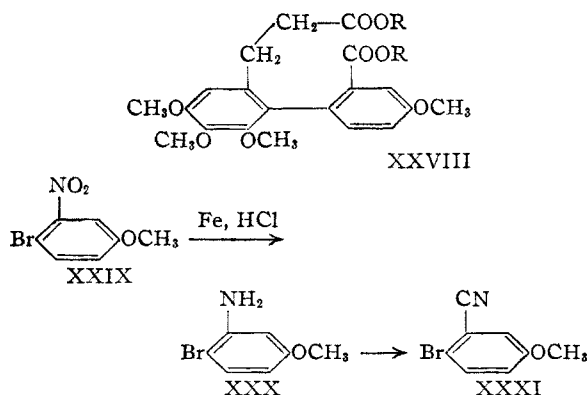


yield and erratic character of the reaction made it impractical for further synthetic operations. By



using nitrobenzene as solvent for the ring-closure¹ a small yield of crystalline product was obtained which had the percentage composition expected of the bromo ketone XXVI.^{14a}

The difficulties mentioned above in the cyclization caused some effort to be spent on the synthesis of XXVIII, which could be converted to the desired ketone VI by a Dieckmann ring-closure.



Some of the intermediates prepared for the synthesis of this compound will be described briefly.

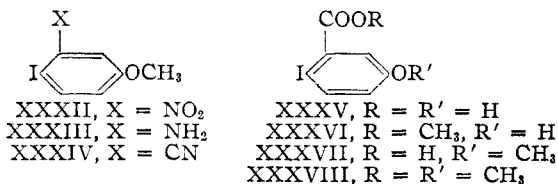
3-Nitro-4-bromoanisole XXIX^{1,15} was reduced

(14a) Note added in proof: H. T. Huang in these laboratories recently has found that the bromo ketone obtained in this way possesses a five-membered ring. Work is being continued to determine the nature of the reaction.

(15) Hodgson and Dyson, *J. Chem. Soc.*, 947 (1935).

with iron powder and acid and converted into the nitrile XXXI; the compound, however, was unchanged by refluxing with copper powder at 270° .

The preparation of the corresponding iodo compound was accordingly undertaken. 3-Nitro-4-iodoanisole¹⁶ was prepared by a modified procedure, and the nitro group reduced with iron and acid. The crude amino compound XXXIII exploded violently during distillation, and attempts



to prepare a number of derivatives from the crude product failed. The nitrile XXXIV was obtained from the crude amine by the Sandmeyer method, but in such small yield as to preclude further synthetic work.

The iodination of *m*-hydroxybenzoic acid, reported¹⁷ to give 2-iodo-5-hydroxybenzoic acid XXXV, yielded in our hands 4-iodo-3-hydroxybenzoic acid¹⁸; the desired 2-iodo acid XXXV was obtained by a modification of the method of Brenans and Prost,¹⁸ but methylation of the acid to the ether-ester XXXVIII proved extremely troublesome. The usual methods of methylation yielded only the carboxylic ester XXXVI. The desired product was finally obtained by treating the phenolic acid XXXV with a large excess of ethereal diazomethane over a period of several days.

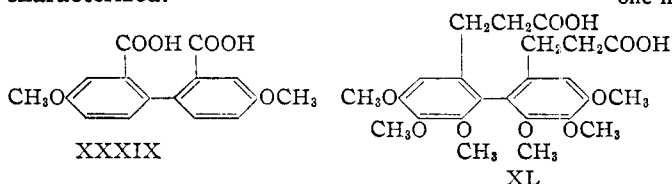
The crossed Ullmann reaction between XXXVIII and the iodotrimethoxyphenylpropi-

(16) Hata, Tatamatsu and Kubota, *Bull. Chem. Soc. Japan*, 10, 425 (1935); *Chem. Zentr.*, 107, I, 546 (1936).

(17) Datta and Prosad, *This Journal*, 89, 448 (1917).

(18) (a) Brenans and Prost, *Compt. rend.*, 178, 1285 (1924); (b) Henry and Sharp, *J. Chem. Soc.*, 856 (1935).

onic ester XX has not yielded the unsymmetrical product XXVIII; the two symmetrical acids XXXIX and XL have however been obtained and characterized.



Acknowledgment.—We are indebted to Dr. Virgil Boekelheide for his interest and helpful suggestions during this work.

Experimental¹⁹

3,4,5-Trimethoxybenzoic acid was prepared by methylating gallic acid.²⁰

***p*-Iodoanisole.**²¹—A solution of 337 g. (3.12 moles) of anisole in 300 cc. of glacial acetic acid was stirred with cooling, while 508 g. (3.12 moles) of iodine monochloride was added during fifteen minutes. The reaction was completed by refluxing gently for two hours. The product was washed with an excess of sodium hydroxide solution containing a small amount of sodium sulfite. The colorless product was distilled through a Vigreux column, giving a forerun of 93 g. of material, and 459 g. of pale amber liquid, b. p. 70–78° (3 mm.). This partly solidified at room temperature, and, upon warming with 400 cc. of methanol, followed by cooling to 0°, yielded 337 g. (46%) of large white crystals of *p*-iodoanisole, m. p. 50–51°.

4,5,6,4'-Tetramethoxybiphenyl-2-carboxylic Acid (VII).—To 10 g. of methyl 2-bromo-3,4,5-trimethoxybenzoate²² dissolved in 30–40 g. of *p*-iodoanisole in a large test-tube was added 25 g. of copper bronze. The mixture was immersed in a metal-bath held at 250–260° and stirred vigorously. After ten to fifteen minutes, when the mass had become too viscous for stirring, heating was continued at 260–265° for about twenty minutes. The hot reaction mixture was then transferred to a beaker, broken up, cooled and extracted repeatedly with acetone or benzene. The extracts were evaporated to dryness in a stream of air, taken up in methanol, and saponified by adding aqueous alkali to the refluxing solution. After two to three hours, when the saponification was complete, water was added and the alcohol removed by evaporation. After cooling the solution, 4,4'-dimethoxybiphenyl and unchanged iodoanisole were removed by filtration, and the filtrate shaken with Raney nickel and hydrogen at 3 atm. for three hours.²³ After removal of the catalyst by centrifugation, excess anisole present was removed by steam distillation and the residue carefully acidified. The combined oily acids were extracted with boiling water to remove trimethoxybenzoic acid. The residue was extracted with boiling benzene, which left undissolved the symmetrical 3,4,5,3',4',5'-hexamethoxybiphenyl-2,2'-dicarboxylic acid of m. p. 252–253°.²⁴ The benzene extract was evaporated to dryness, leaving a residue of the desired acid VII, which, recrystallized from alcohol, melted at 163.5–164.5°, solidifying and remelting at 173–174°. The yield was 25–37%. *Anal.* Calcd. for C₁₇H₁₈O₈: C, 64.14; H, 5.70. Found: C, 64.20; H, 5.66.

(19) Melting points corrected; microanalyses by the Micro-Tech Laboratories.

(20) "Organic Syntheses," Coll. Vol. I, 2nd Ed., p. 537.

(21) Cf. Blicke and Smith, *THIS JOURNAL*, **50**, 1229 (1928).

(22) Bogert and Plaut, *ibid.*, **37**, 2726 (1915).

(23) For this method of purifying products of an Ullmann reaction, cf. Carlin, *THIS JOURNAL*, **67**, 928 (1945).

(24) Herzig and Polak (*Monatsh.*, **29**, 270 (1908)) report a m. p. of 240° for this acid.

3,4,5-Trimethoxy-2-(4-methoxyphenylazo)-benzoic Acid (XII).—One mole of *p*-anisidine in a solution containing two moles of hydrochloric acid was diazotized at 0° with sodium nitrite. One mole of sodium acetate and one mole of the sodium salt of trimethoxybenzoic acid in the minimum volume of water were added to the diazonium solution and the mixture warmed up to room temperature. The acidic, orange azo-compound XII was obtained by acidifying the mixture, collecting the precipitate by filtration and washing the filter cake with methyl alcohol. The residue on the funnel, after recrystallization from ethanol or acetic acid, melted at 221°. *Anal.* Calcd. for C₁₇H₁₈O₈N₂: C, 58.95; H, 5.24. Found: C, 58.88; H, 5.31. From the methanol washings unchanged trimethoxybenzoic acid was isolated.

2,3,4,7-Tetramethoxyfluorenone (XI).—A solution of 1 g. of 4,5,6,4'-tetramethoxybiphenyl-2-carboxylic acid VII in 5 cc. of dry benzene was treated with the calculated amount of phosphorus pentachloride and refluxed for two hours. The reaction mixture was extracted with hot sodium bicarbonate solution and the benzene evaporated. The residue was crystallized from ethanol, giving orange-red needles of the fluorenone, m. p. 117–118°. *Anal.* Calcd. for C₁₇H₁₆O₅: C, 67.99; H, 5.37. Found: C, 67.97; H, 5.37. The fluorenone was also obtained when the evaporation of the phosphorus oxychloride present was attempted in high vacuum.

2-Carbomethoxy-4,5,6,4'-tetramethoxybiphenyl (X), obtained from the acid VII with ethereal diazomethane, crystallized from dilute alcohol as colorless plates, m. p. 63°. *Anal.* Calcd. for C₁₈H₂₀O₆: C, 65.05; H, 6.07. Found: C, 65.08; H, 6.08. Two grams of the ester in 20 cc. of alcohol were refluxed for two hours with 1 cc. of hydrazine hydrate: on cooling, crystals of m. p. 81° separated, which were insoluble in dilute acid. *Anal.* Calcd. for C₁₇H₂₀N₂O₅ (the hydrazide): C, 61.43; H, 6.07. Calcd. for C₃₄H₃₈N₂O₁₀ (the bis-hydrazide): C, 64.54; H, 5.74. Found: C, 64.66, 64.84; H, 6.66, 6.61.

3,4,5-Trimethoxybenzaldehyde (XV) was prepared in 30–50% yield by the Rosenmund reduction of 3,4,5-trimethoxybenzoyl chloride.²⁵

3,4,5-Trimethoxybenzyl 3,4,5-Trimethoxybenzoate (XVI).—From some runs of the Rosenmund reduction, 3,4,5-trimethoxybenzoic anhydride, m. p. 160°,²⁶ and a product of m. p. 107° previously obtained by Späth and Mauthner¹¹ were isolated; the latter, insoluble in water and alkali, and unaffected by permanganate in boiling water, was saponified with alcoholic alkali. 3,4,5-Trimethoxybenzoic acid, m. p. 171°, and 3,4,5-trimethoxybenzyl alcohol (3,5-dinitrobenzoate, m. p. 147°¹⁰) were isolated from the saponification reaction. The compound of m. p. 107° is therefore the ester XVI. *Anal.* Calcd. for C₂₀H₂₄O₈: C, 61.22; H, 6.17. Found: C, 60.81; H, 6.03.

Isopropyl 3,4,5-Trimethoxythiolbenzoate.—This compound was prepared to see if the desulfuration procedure²⁷ could be used to obtain 3,4,5-trimethoxybenzaldehyde. A solution of 12.04 g. of trimethoxybenzoyl chloride and 7.4 g. (100% excess) of isopropylmercaptan in 30 cc. of pyridine was heated on the steam-bath for one hour. The product was obtained in 89% yield (crude), and, after recrystallization for analysis from aqueous methanol, melted at 47–48°. *Anal.* Calcd. for C₁₃H₁₈O₄S: C, 57.75; H, 6.70. Found: C, 57.96; H, 6.80.

A 4-g. portion of the thiol ester was refluxed with 25 g. of freshly prepared Raney nickel²⁸ in 100 cc. of 70% alcohol for twenty-four hours. The product was 1.97 g. of an oil which did not give an aldehyde test with dinitrophenylhydrazine reagent. The oil gave a poor yield of 3,4,5-trimethoxybenzyl 3,5-dinitrobenzoate, m. p. 143.5–

(25) Nierenstein, *J. prakt. Chem.*, **132**, 200 (1931); cf. Slotta, *ibid.*, **133**, 129 (1932).

(26) Sharp, *J. Chem. Soc.*, 1234 (1936).

(27) Wolf from and Karabinos, *THIS JOURNAL*, **68**, 1455 (1946).

(28) Pavlic and Adkins, *ibid.*, **68**, 1471 (1946).

146.5° (reported,¹⁰ 147–148°).²⁹ In other runs, using old Raney nickel in refluxing 70% alcohol, or shaking with fresh nickel at room temperature, unreacted ester was the only product obtained.³⁰

3,4,5-Trimethoxycinnamic acid (XVII) was prepared by the procedure of Slotta and Heller,⁹ by condensing the aldehyde with malonic acid in pyridine with 1% of piperidine as catalyst.

β -(3,4,5-Trimethoxyphenyl)-propionic Acid (XVIII).—A solution of 10 g. of 3,4,5-trimethoxycinnamic acid in 50 cc. of water and the calculated amount of sodium hydroxide was shaken for three hours with hydrogen at 4 atm. in the presence of Raney nickel. The catalyst was removed by filtration, the solution was cooled in ice and carefully acidified. The crystalline acid of m. p. 104° separated from the solution in practically quantitative yield. The previously reported m. p.'s are 98°⁹ and 100–102°.¹⁰

β -(2-Iodo-3,4,5-trimethoxyphenyl)-propionic Acid (XIX).—To a solution of 50 g. of the trimethoxyphenyl-propionic acid XVIII in 75 cc. of acetic acid and 300 cc. of water at 40° was added a 20% excess of iodine monochloride. After the exothermic reaction had subsided, the reaction mixture was allowed to stand for another hour, then decolorized with sodium bisulfite, and diluted with water to 800 cc. The iodo acid separated in 95% yield as granular crystals, which were purified by dissolving in sodium carbonate and reprecipitating from about 600 cc. of solution with hydrochloric acid. Crystallization from carbon tetrachloride or dilute methanol gave material of m. p. 124–125°. *Anal.* Calcd. for $C_{12}H_{13}IO_5$: C, 39.36; H, 4.13; neut. equiv., 366. Found: C, 39.00; H, 4.09; neut. equiv., 369. This method of iodination was far superior to that employing iodine and mercuric oxide, which was also used.

The methyl ester (XX) was obtained from the acid with ethereal diazomethane. After removal of the ether, the ester was used directly in the Ullmann reaction. An analytical sample, purified by vacuum distillation, had b. p. 175° (2.5 mm.), m. p. 36–37.5°. *Anal.* Calcd. for $C_{13}H_{17}IO_5$: C, 41.07; H, 4.51. Found: C, 41.00; H, 4.72.

β -2-(4,5,6,4'-Tetramethoxybiphenyl)-propionic Acid (V).—An Ullmann reaction between methyl β -(2-iodo-3,4,5-trimethoxyphenyl)-propionate (XX) and *p*-iodoanisole was carried out by a procedure similar to that described above for compound VII. The iodo ester (3.6 g.), *p*-iodoanisole (20 g.) and copper bronze (10 g.) were heated with stirring for one-half to one hour at 250–255°, and the products worked up as before. The aqueous solution of the saponified products was acidified, the oily acids taken up in benzene, and the fine needles, which formed almost immediately, were recrystallized from benzene; the product retained benzene of crystallization very tenaciously. The acid was very soluble in alcohol and acetone, slightly soluble in carbon tetrachloride, and melted, after crystallization from dilute ethanol, at 106.5–107°. *Anal.* Calcd. for $C_{19}H_{18}O_6$: C, 65.88; H, 6.40. Found: C, 65.58; H, 6.34.

β -2-(3-Bromo-4,5,6,4'-tetramethoxybiphenyl)-propionic Acid (XXI).—To 6 g. of the biphenylpropionic acid V in 10 cc. of acetic acid at 0–5° was added dropwise with stirring a solution of 3 g. of bromine in 10 cc. of acetic acid. The mixture was allowed to stand for several hours at room temperature, then an equal volume of water was added. The crystalline acid, which separated on cooling in ice, was collected and dissolved in hot saturated sodium bicarbonate solution. From this, the crystalline sodium salt precipitated on cooling. The salt was collected, dissolved in hot water and converted to the acid by adding

mineral acid. The purified acid, after crystallization from ethanol, melted at 169–171°. *Anal.* Calcd. for $C_{19}H_{17}BrO_5$: C, 53.67; H, 4.98. Found: C, 53.67; H, 4.88.

The methyl ester (XXII) was prepared from the acid with ethereal diazomethane or by heating the dry sodium salt with dimethyl sulfate for thirty minutes on the steam-bath. Crystallization from methanol gave a product melting at 92–93°. *Anal.* Calcd. for $C_{20}H_{23}BrO_5$: C, 54.68; H, 5.28. Found: C, 54.85; H, 5.73. The methyl ester in methanol solution was heated with hydroxylamine and dilute sodium hydroxide on the steam-bath for ten minutes, cooled, filtered and saturated with carbon dioxide. The hydroxamic acid which precipitated melted at 172–173°, dec.; for analysis, see below.

β -(2-Bromo-3,4,5-trimethoxyphenyl)-propionic Acid XXIII.—A solution of 1.60 g. of bromine in 5 cc. of glacial acetic acid was added slowly to 2.4 g. of trimethoxyphenylpropionic acid XVIII in 5 cc. of acetic acid, cooled in an ice-bath. The solution was allowed to stand for two hours at room temperature, until the color of bromine had disappeared, and 10 cc. of water was then added. On cooling in the refrigerator, crystals separated; a second crop was obtained by diluting with more water. β -(2-Bromo-3,4,5-trimethoxyphenyl)-propionic acid, crystallized from carbon tetrachloride–petroleum ether, had the m. p. 92.5–93.5°. *Anal.* Calcd. for $C_{12}H_{11}BrO_5$: C, 45.16; H, 4.74; neut. equiv., 319. Found: C, 45.06; H, 4.65; neut. equiv., 322.

β -(2,6-Dibromo-3,4,5-trimethoxyphenyl)-propionic acid was prepared from XVIII for reference in the same manner as the monobromo acid XXIII, except that an excess of bromine in acetic acid was added. When the reaction was complete, the excess of bromine was reduced with sodium bisulfite solution. The dibromo acid may be purified through its sodium salt, which is only slightly soluble in cold water. The free acid, recrystallized from benzene–petroleum ether, melted at 119.5°, then solidified and remelted at 122°. *Anal.* Calcd. for $C_{12}H_9Br_2O_5$: C, 36.22; H, 3.54. Found: C, 36.46; H, 3.55.

β -(2-Bromo-6-iodo-3,4,5-trimethoxyphenyl)-propionic Acid XXIV.—A solution of 1.3 g. of the bromo acid XXIII in 3 cc. of acetic acid was treated with excess of iodine monochloride in acetic acid in the cold. The solution was slowly warmed on the water-bath, then cooled, and the excess halogen removed with bisulfite. On dilution with water, the iodobromo acid precipitated in fine plates. The acid was purified by crystallizing the slightly water-soluble sodium salt from benzene, then regenerating the acid. Final crystallization from dilute ethanol yielded an acid of m. p. 130–132°. The product was not analytically pure, but the presence of iodine and bromine is borne out by the analysis. *Anal.* Calcd. for $C_{12}H_9IO_5Br$: C, 32.38; H, 3.17. Found: C, 33.95; H, 3.27.

β -2-(3-Bromo-4,5,6,4'-tetramethoxybiphenyl)-propionic Acid XXI by the Ullmann Reaction.—The methyl ester of the above acid XXIV (0.4 g.) was heated with copper powder (2.5 g.) and *p*-iodoanisole (3 g.) for fifteen minutes at 250–260°. The mixture was extracted and saponified as in previous Ullmann reactions. The acids liberated consisted of a mixture of product and starting material, and were separated by the differential solubility of their dry sodium salts in benzene. The combined sodium salts were taken up in hot benzene. On cooling to room temperature the salt of the phenylpropionic acid XXIV precipitated out completely, leaving most of the biphenylpropionic acid XXI in solution. On evaporation of the solution and acidification, crystals were obtained (from ethanol) of m. p. 169–171°, giving no depression of mixed melting point with acid XXI prepared by the procedure described above.

Cyclization Experiments on the Acid XXI.—Only the following experiments are described in any detail; other methods tried are listed in the introduction.

With Phosphorus Oxychloride.—To 1 g. of the acid in 50 cc. of benzene (or toluene) was added the calculated weight of phosphorus pentachloride for conversion to the acid chloride. The reaction mixture was refluxed for four hours, then cooled and extracted with cold concentrated

(29) Prelog and co-workers (*Helv. Chem. Acta*, **29**, 360, 684 (1946)) have observed reduction of thiol esters to primary alcohols by refluxing with Raney nickel.

(30) This work was carried out before the appearance of the paper by Spero, McIntosh and Levin, *This Journal*, **70**, 1907 (1948), describing the use of partially deactivated Raney nickel for this reaction.

sodium bicarbonate solution. The residue from the organic layer was treated for an hour with hot concentrated sodium bicarbonate solution. A small amount of neutral oil, which remained undissolved, was crystallized from methanol, and melted at 91.5–92.5°; it gave no depression on mixed m. p. with the methyl ester XXII described above.

The hydroxamic acid, prepared as above, gave no depression on mixed m. p. with the authentic sample, and melted at 172–173°, dec. *Anal.* Calcd. for $C_{19}H_{23}BrNO_3$: N, 3.18. Found: N, 3.63. Both the ester and the hydroxamic acid yielded acid XXI on saponification.

With Aluminum Chloride.—A solution of the acid XXI (1 g.) in tetrachloroethane (50 cc.) was treated with the calculated weight of phosphorus pentachloride. The solution was heated to 80° for ten minutes to bring about complete conversion to the acid chloride and thereupon cooled to –10 to –5° in an ice-salt mixture. To the cold solution was added 0.33 g. of finely powdered aluminum chloride, some of which failed to go into solution despite vigorous agitation. The mixture, after being heated at 90° for ten minutes, was poured into 50 g. of ice and 10 cc. of concentrated hydrochloric acid to extract aluminum salts. The organic layer, after being washed with aqueous sodium bicarbonate, was evaporated at reduced pressure, and the residue extracted for one to two hours with hot concentrated sodium bicarbonate solution. The oily neutral residue (100–150 mg.) yielded in one case crystals of m. p. 141–144° from ethanol. The crude product yielded a semicarbazone, crystallized from ethanol, m. p. 210–212°, dec. *Anal.* Calcd. for $C_{19}H_{23}BrN_2O_3$: C, 51.85; H, 4.78; N, 9.05. Calcd. for $C_{19}H_{23}N_2O_3$: C, 62.32; H, 6.01; N, 10.90. Found: C, 59.62; H, 5.68; N, 11.24.

An oxime was also obtained which, crystallized from chloroform-ethanol, had m. p. 209–212°. Other fractions had m. p. 206–217°. *Anal.* Calcd. for $C_{19}H_{23}NO_3$: C, 54.04; H, 4.77. Calcd. for $C_{19}H_{23}NO_3$: C, 66.46; H, 6.17. Found: C, 65.46; H, 5.98.

In Nitrobenzene.—To 1 g. of the biphenylpropionic acid XXI in 25 cc. of nitrobenzene was added 0.5 g. of phosphorus pentachloride, the mixture being warmed to 80° to complete formation of the acid chloride. After cooling to 0°, 0.33 g. of aluminum chloride was added and the solution swirled vigorously. Heating for five minutes in a bath at 90° dissolved the aluminum chloride. The product was purified by extracting the nitrobenzene layer repeatedly with cold dilute hydrochloric acid and then with hot sodium bicarbonate solution. The dried organic layer was freed from solvent by vacuum distillation. The bromo ketone of m. p. 145° was obtained on crystallization from ethanol. *Anal.* Calcd. for $C_{19}H_{21}O_3Br$: C, 56.03; H, 4.70. Found: C, 55.88; H, 5.03.

An oxime, prepared from a less pure sample of ketone, gave a poor analysis for carbon.

4-(*p*-Methoxyphenyl)-5,6,7-trimethoxyhydrindone (XXVII).—A solution of 0.88 g. of β -(2-(4,5,6,4'-tetramethoxy)-biphenyl)-propionic acid in 25 cc. of tetrachloroethane was treated with the calculated weight of phosphorus pentachloride. After addition to the ice-cold solution of 0.33 g. of aluminum chloride, the mixture was swirled for ten minutes while immersed in an oil-bath at 90°. After decomposition of the reagents, removal of the solvent, and extraction with dilute alkali, there remained 0.24 g. of a compound, m. p. 86°, which when crystallized from ethanol, formed stout needles of m. p. 89°. The acid was not cyclized by anhydrous hydrofluoric acid. *Anal.* Calcd. for $C_{19}H_{23}O_6$: C, 69.50; H, 6.14. Found: C, 69.70; H, 5.94. The oxime crystallized in colorless prisms, m. p. 217°, dec., from a mixture of ethanol and chloroform. *Anal.* Calcd. for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.17; N, 4.08. Found: C, 66.24; H, 6.01; N, 4.46.

3-Amino-4-bromoanisole XXX.—A 23.2-g. portion of 3-nitro-4-bromoanisole^{14,31} (0.1 mole) in 100 cc. of 50% alcohol, and 17 g. (0.3 mole) of iron powder (J. T. Baker

purified by hydrogen) were heated to refluxing on the steam-bath and stirred with a tantalum Hershberg stirrer, while 1.2 cc. of concentrated hydrochloric acid was added dropwise. The addition was very slow at first, and a vigorous reaction ensued. After all of the acid had been added, refluxing and stirring were continued for several hours. The solid material was removed from the hot product by centrifuging, the clear solution was brought to a slightly alkaline reaction with potassium hydroxide, and the flocculent precipitate was centrifuged down. The solution was boiled until a heavy oil separated and commended to steam distill. The oil was taken up in benzene, the solution clarified by centrifuging, the solvent removed by flash-distillation and the product distilled, giving 69% (13.9 g.) of pale yellow oil, b. p. 76–98° (2 mm.). The hydrochloride melted, after crystallization from water, at 183.5–184°, dec.³² An attempted selective catalytic reduction of the nitro bromoanisole with hydrogen and platinum³³ was unsuccessful.

2-Bromo-5-methoxybenzonitrile XXXI.—The amine obtained above (13.9 g.) was diazotized and the clear dark red diazonium solution was poured into an ice-cold solution, which had been prepared by dissolving 9.3 g. of cuprous cyanide and 15.3 g. of sodium cyanide in 40 cc. of water. A thick brown mass was formed, and hydrogen cyanide was evolved; the mixture was heated on the steam-bath with stirring until a heavy oil settled out. This was taken up in 200 cc. of benzene, washed with dilute sodium hydroxide and hydrochloric acid, clarified by centrifuging, the solvent removed and the residue distilled at 2 mm., with precautions to prevent solidification in the side arm. A slightly yellow solid (8.2 g., 56%) was obtained, m. p. 84–97°. After crystallization from benzene an analytical sample was obtained as long, colorless needles, m. p. 98.5–99.5°. *Anal.* Calcd. for C_8H_7BrNO : C, 45.31; H, 2.85. Found: C, 45.41; H, 2.84. Hydrolysis of the nitrile with potassium hydroxide in diethylene glycol yielded 2-bromo-5-methoxybenzoic acid, m. p. 157–158°. A portion of the nitrile was heated at the reflux temperature (about 270°) with copper bronze. The metal remained bright and no reaction seemed to occur.

3-Nitro-4-iodoanisole XXXII.—The published procedure¹⁶ was modified as follows. A suspension of 44 g. of finely divided 3-nitro-4-aminoanisole in 250 cc. of ice and water was diazotized at –5°. The diazonium solution was poured into a cold solution of 65 g. (50% excess) of potassium iodide in 65 cc. of water. Heat and gases were evolved, and the mixture was heated on the steam-bath until a heavy oil separated, which solidified on cooling. It was taken up in benzene, washed with concentrated hydrochloric acid and with dilute sodium hydroxide solution containing a little sodium sulfite; after evaporation of the benzene, a 90% yield of crude material was obtained, which formed fine orange needles, m. p. 60.5–61.5° after crystallization from aqueous methanol.

3-Amino-4-iodoanisole (XXXIII).—Reduction of the nitro compound XXXII with iron and hydrochloric acid, by the method described above for the bromo compound, gave, in a small run, 52% yield of a red oil, b. p. 92–112° (0.2 mm.). Repetition of the reaction on a 1 mole scale was terminated by a violent explosion during the vacuum distillation.

The only crystalline compound that could be obtained from the crude aminoiodoanisole was the nitrile below. Reduction of the 3-nitro-4-iodoanisole with stannous chloride, with ferrous hydroxide in ammonium hydroxide, or electrolytically, yielded either *m*-anisidine or intractable products.

2-Iodo-5-methoxybenzonitrile XXXIV.—The crude amine (5.7 g.) was diazotized and added to a solution of 4.03 g. of cuprous cyanide and 6.75 g. of sodium cyanide

(32) The reported value¹⁴ is 186°; the reduction was carried out previously,¹⁵ but details were not given.

(33) Cf. Adams, Cohen and Rees, *THIS JOURNAL*, 49, 1093 (1927).

(34) Pechorr, *A. M.*, 391, 26 (1912), reports a m. p. of 161–162° for this compound.

(31) Samant, *Ber.*, 75, 1008 (1942).

n 20 cc. of water. The mixture was heated on the steam-bath, the heavy oil which separated was taken up in benzene, washed with acid and base, and the benzene was evaporated. The black tar remaining was subjected to vacuum sublimation, yielding a mushy yellow solid, which on resublimation and crystallization from benzene-petroleum ether, formed colorless plates, m. p. 98–100°. *Anal.* Calcd. for C_8H_5INO : C, 37.09; H, 2.34. Found: C, 37.46; H, 2.43.

3-Hydroxy-4-iodobenzoic Acid.—This reaction is described because this procedure is reported¹⁷ to yield 2-iodo-5-hydroxybenzoic acid XXXV. A solution of 13.8 g. of *m*-hydroxybenzoic acid in 200 cc. of concentrated ammonium hydroxide was stirred while a solution of 23.4 g. of iodine and 18.2 g. of potassium iodide in 100 cc. of water was added during five minutes. A precipitate of nitrogen triiodide was formed and reacted rapidly. The resulting green solution was stirred for an additional ten minutes and acidified to congo red by adding 180 cc. of concentrated hydrochloric acid. The thick precipitate was collected, and crystallized from a mixture of 100 cc. of water and 20 cc. of alcohol, giving a nearly quantitative yield of white needles, m. p. 225–227° dec; the acetyl derivative melted at 199.5–201.5°. The product was therefore the 3-hydroxy-4-iodobenzoic acid, which is reported^{18a} to melt at 226° (acetyl derivative, 203°), and not the 2-iodo-5-hydroxy isomer.

2-Iodo-5-hydroxybenzoic Acid (XXXV).—The procedure of Brenans and Prost^{18a} was modified as follows. An ice-cold solution of benzenediazonium chloride prepared from 37.2 g. of aniline was added with stirring to a solution of 55.2 g. of *m*-hydroxybenzoic acid and 48 g. of sodium hydroxide in 400 cc. of water. A sticky orange-red precipitate formed which dissolved on warming to 50°, the dark red solution was heated and stirred while a solution of 144 g. of sodium hydroxide in 150 cc. of water was added, followed by 210 g. of solid sodium hydrosulfite. With the solution at 80–90°, more sodium hydrosulfite was added in 5-g. portions at one-minute intervals until the dark red color was discharged. The solution was cooled to 30°, 500 g. of ice was added and the solution brought to a pH of 5.5 with concentrated hydrochloric acid. The pale yellow precipitate of 2-amino-5-hydroxybenzoic acid was collected, and diazotized at 0° with 67 cc. of concentrated sulfuric acid, 400 g. of ice and 26 g. of sodium nitrite. The diazonium solution was poured into a solution of 84 g. of potassium iodide in 150 cc. of water; the reaction which ensued was completed by heating on the steam-bath for an hour. Cooling to 0° gave 67.6 g. (84%) of dark purple crystalline product, which was purified by boiling with 15 g. of Nuchar in 700 cc. of water for an hour. Cooling to 0° yielded 52 g. (49% over-all from *m*-hydroxybenzoic acid) of nearly white needles which melted to a red liquid at 201–202.5°. The reported^{18a} m. p. is 196–198°.

Methyl 2-iodo-5-hydroxybenzoate (XXXVI) was obtained from the acid with a slight excess of ethereal diazomethane solution. The product was isolated by vacuum sublimation followed by crystallization from benzene-petroleum ether; it formed white granular crystals, m. p. 102–103°. *Anal.* Calcd. for $C_8H_7IO_3$: C, 34.55; H, 2.54. Found: C, 34.90; H, 2.72.

Methyl 2-iodo-5-methoxybenzoate (XXXVIII) was obtained when 2.64 g. of 2-iodo-5-hydroxybenzoic acid was treated with a five-fold excess of ethereal diazomethane,

and allowed to stand several days. The solution was washed with sodium hydroxide, dried, and the ether removed, leaving 1.81 g. (62%) of crude ester. This was distilled at 150° (0.8 mm.), giving a very pale yellow oil, n_D^{20} 1.6000. *Anal.* Calcd. for $C_9H_9IO_3$: C, 37.01; H, 3.11. Found: C, 37.34; H, 3.27. Hydrolysis of this compound yielded 2-iodo-5-methoxybenzoic acid (XXXVII), which could not be obtained analytically pure; apparently there was some loss of iodine during saponification.

4,4'-Dimethoxydiphenic Acid (XXXIX).—A 1.00-g. portion of methyl 2-iodo-5-methoxybenzoate was mixed with 1.00 g. of copper bronze, and heated at 280–300° for twenty minutes. The product was extracted with two 7 cc. portions of benzene, which, on evaporation, yielded a dark oil. This was saponified with Claisen alkali; acidification produced a brown precipitate which was refluxed with Nuchar in aqueous methanol until the color had been removed. Upon cooling, a white powder was obtained which was crystallized from nitrobenzene; the fine white crystals melted at 245–248° on the heated stage. *Anal.* Calcd. for $C_{14}H_{14}O_6$: C, 63.57; H, 4.67. Found: C, 63.78; H, 4.84.

2,2',3,3',4,4'-Hexamethoxy-6,6'-di-(β -carboxyethyl)-biphenyl (XL).—Methyl β -(3,4,5-trimethoxy-2-iodophenyl)-propionate (1.5 g.) and 1.5 g. of copper dust were heated in a test-tube in a Wood's metal bath at 265–270° for twenty minutes. The product was extracted with hot benzene, the extract was evaporated on the steam-bath and the residue was saponified by heating with Claisen alkali. Acidification gave an amber oil which was vacuum sublimed. A portion of the sublimate was crystallized from aqueous acetic acid, when it formed a white powder which sintered at 188–189° and melted to an amber liquid at 189–193°. *Anal.* Calcd. for $C_{24}H_{20}O_{10}$: C, 60.24; H, 6.32. Found: C, 59.98; H, 6.06.

Crossed Ullmann Reaction.—A mixture of equivalent quantities of methyl β -(3,4,5-trimethoxy-2-iodophenyl)-propionate and methyl 2-iodo-5-methoxybenzoate was heated with copper powder and the reaction product was converted to the free carboxylic acids in the usual way. The material thus obtained was subjected to an eight-plate multiple countercurrent extraction, using ether and 2 *M* phosphate buffer of pH 5.9 in 60-cc. separatory funnels.³⁵ The two symmetrical reaction products were separated in this way, but none of the desired unsymmetrical acid was obtained.

Summary

β -2-(3-Bromo-4,5,6,4'-tetramethoxybiphenyl)-propionic acid has been synthesized, its structure proved, and its ring-closure to the bromo ketone studied. 4,5,6,4'-Tetramethoxybiphenyl-2-carboxylic acid has been prepared, and found to cyclize spontaneously to the fluorenone, when converted to the acid chloride. A number of new compounds have been prepared and characterized in connection with these syntheses.

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(35) Craig, Hogeboom, Carpenter and du Vigneaud, *J. Biol. Chem.*, **168**, 669 (1947), and earlier papers.