

A crossed Ullmann reaction of methyl β -(2-iodo-3,4,5-trimethoxyphenyl)-propionate and excess 4-bromo-3-nitroanisole yielded β -[2-(4,5,6,4'-tetramethoxy-2'-nitro)-biphenyl]-propionic acid (I), which was readily reduced to the corresponding amino compound (II). When II was diazotized and treated with cuprous cyanide under conditions calculated to yield the nitrile III, only 1-(β -carboxyethyl)-3,4,7-trimethoxydibenzofuran (V) was obtained. The formation of dibenzofuran from 2-amino-2'-methoxybiphenyl³ and of 3,4,7-trimethoxydibenzofuran from 2,3,4,4'-tetramethoxy-2'-aminophenyl⁴ under similar conditions has been reported.

The structure assigned to V is supported by a comparison of its absorption spectrum with that of 3,4,7-trimethoxydibenzofuran and compounds I and II as shown in Fig. 1. The spectrum of each dibenzofuran derivative exhibits a maximum near 300 m μ which has the same extinction coefficient as the corresponding maximum at 260 m μ . In the case of the biphenyl derivatives I and II, the extinction coefficients of the higher and lower wave length maxima differ greatly.

Experimental⁵

β -[2-(4,5,6,4'-Tetramethoxy-2'-nitro)-biphenyl]-propionic Acid (I).—A mixture of 7.60 g. (0.02 mole) of methyl β -(2-iodo-3,4,5-trimethoxyphenyl)-propionate and 27.8 g. (0.12 mole) of 4-bromo-3-nitroanisole was heated at 220–255° while 20 g. of electrolytic copper dust was added in small portions with stirring. The product was extracted with six 25-cc. portions of benzene. Evaporation of the benzene gave a red-brown tar which was refluxed for an hour with 25 cc. of Claisen alkali. Fifty cc. of water was added and the mixture was centrifuged to remove 4,4'-dimethoxy-2,2'-dinitrobiphenyl. Acidification of the aqueous solution with hydrochloric acid gave a dark oil which was purified by refluxing with Darco and Celite in aqueous methanol. Cooling and scratching gave a fine, yellow solid which was recrystallized from benzene with the addition of ligroin, when it formed granular, yellow crystals, yield 2.20 g. (28%), m. p. 100–102°.

Anal. Calcd. for C₁₉H₂₁O₈N: C, 58.30; H, 5.41. Found: C, 58.31; H, 5.54.

β -[2-(2'-Amino-4,5,6,4'-tetramethoxy)-biphenyl]-propionic Acid (II).—A portion of the nitro compound in

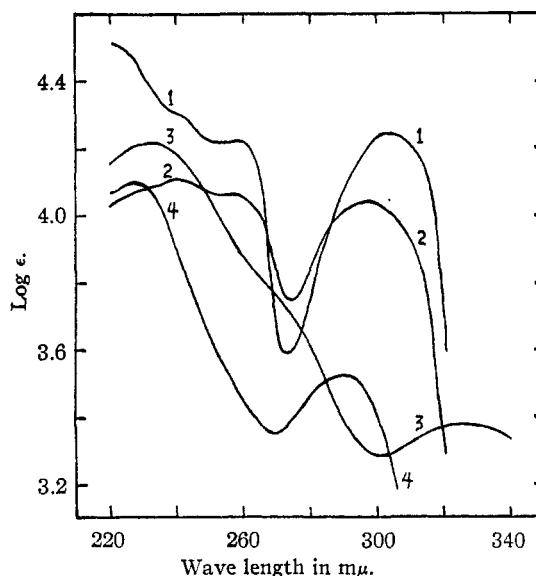


Fig. 1.—Molar extinction curves in ethanol: (1) 3,4,7-trimethoxydibenzofuran⁴; (2) dibenzofuran derivative, V; (3) nitrobiphenyl derivative, I; (4) aminobiphenyl derivative, II.

ethanol was shaken for one-half hour with Raney nickel and hydrogen at 1000 lb. and 155°. Evaporation of the solvent and crystallization of the residue from benzene-ligroin gave a light tan crystalline powder, yield 42%, m. p. 125.5–126°.

Anal. Calcd. for C₁₉H₂₁O₈N: C, 63.15; H, 6.41. Found: C, 64.95; H, 6.61.

1-(β -Carboxyethyl)-3,4,7-trimethoxydibenzofuran (V).—A 360-mg. (0.001 mole) portion of the amino acid II was dissolved in a mixture of 10 cc. of water and 10 drops of sulfuric acid and diazotized at –5° by the addition of 74 mg. of solid sodium nitrite. Upon standing for an hour at room temperature gas was evolved and a flocculent orange precipitate separated. The yield of crude product melting at 132–145° was 76%. Crystallization from dilute methanol gave 191 mg. (58%) of tan needles, m. p. 146–148°. An analytical sample, m. p. 148°, was obtained by successive recrystallization from dilute methanol (Darco) and benzene.

Anal. Calcd. for C₁₈H₁₈O₈: C, 65.45; H, 5.49. Found: C, 65.16; H, 5.29.

The same product was obtained in lower yield when the diazonium solution was poured into a solution of cuprous cyanide in aqueous sodium cyanide.

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The Fluorination of Periodic Acid

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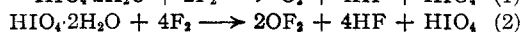
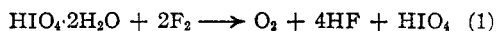
As part of the research now under way to produce compounds in which the hydrogen atoms of acids have been replaced by fluorine, the study of the reaction of fluorine with periodic acid was undertaken. Fluorination of both solid HIO₄·2H₂O and KIO₄ as well as an aqueous or sulfuric acid solution of the acid were carried out, but the desired compound fluorine periodate was not obtained. The reaction of fluorine with HIO₄·2H₂O

(3) Mascarelli and Pirona, *Gazz. chim. ital.*, **68**, 117 (1938); *C. A.*, **32**, 6235 (1938).

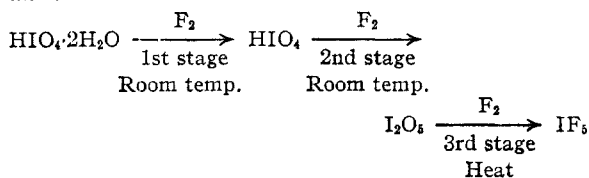
(4) Tarbell, Frank and Fanta, *THIS JOURNAL*, **68**, 502 (1946).

(5) All melting points are corrected and were taken on the heated stage. The microanalyses are by C. W. Beazley, S. M. Nagy and Mrs. O. C. Sauvage. Absorption curves were determined with a Beckmann Spectrophotometer.

was studied in some detail, however, and the complete reaction was found to take place in three stages. As the change commenced, water of hydration was removed from the acid without a change in the valence of iodine according to the equations



In three experiments performed, the percentage of OF_2 in the gaseous product of O_2 and OF_2 varied from about 3 to 27%, the higher percentage being favored by a shorter reaction time. In the second stage, the continued action of fluorine caused the formation of iodine pentoxide, probably as the result of the dehydration of HIO_4 , and in the final step iodine pentafluoride was formed by a reaction which became rapid only at temperatures above 250°C .

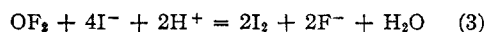


To investigate the first phase of the reaction a copper chamber with a volume of about one-half liter was employed. This was fitted with a brass ground-joint union which had been blanked off and polished to make a tight seal. Acid samples were placed in the reaction chamber which was then evacuated. A known volume of undiluted F_2 gas, freed of HF, was admitted and the course of the subsequent reaction was followed by observing an attached manometer. At the desired time the gas mixture within the reaction vessel was sampled by admitting a portion to an evacuated sample bottle.

Preliminary experiments showed that $\text{HIO}_4 \cdot 2\text{H}_2\text{O}$ could be caused to lose weight upon fluorination without a loss in total oxidizing capacity. However, it was found difficult during the steady fluorination of small samples to prevent some loss in oxidizing capacity before a weight loss had occurred which would correspond to the removal of all the water of hydration. Therefore to study the reaction of fluorine with the water of hydration alone, the described copper chamber was employed and relatively large samples of acid were used. Thus three samples of 3.083, 3.467 and 3.510 g. of the acid were successively fluorinated at room temperature in the apparatus for periods of one and one-third, five and twenty-four hours, respectively. After fluorination under these conditions the total oxidizing capacities were found by iodometric titrations to have been substantially unchanged, indicating that within experimental error there was no reduction in the valence of the iodine.

Gaseous reaction products of the above runs were determined by analysis of samples collected in glass bulbs. It was shown qualitatively that the gases produced were oxygen, oxygen difluoride,

and hydrogen fluoride. They may be considered to have been formed from the water of hydration of the acid by the reactions (1) and (2). Since the hydrogen fluoride was removed from the gas by absorption on sodium fluoride held in a boat near the periodic acid, the observed drop in pressure during the reaction was equal to one-half of the decrease in the partial pressure of the fluorine. The amount of OF_2 was determined by analysis by allowing a sample of the gas to react with a solution of potassium iodide containing an excess of standard hydrochloric acid solution. One-half the equivalent weight of hydrogen ion consumed, as determined by back-titration with sodium hydroxide solution, was taken as equal to the moles of OF_2 in the sample. The following equation for the reaction of OF_2 indicates that this relationship should be correct.



Using the two equations for the reaction of fluorine with water of hydration of the acid, the number of moles of oxygen formed was calculated to equal one-half the moles of fluorine consumed minus the number of moles of OF_2 produced. Likewise the number of moles of HF produced should be equal to 2 times (number of moles of F_2 consumed — number of moles of OF_2 formed). The values so calculated for the moles of HF produced should be equal to those obtained by determining the increase in weight of the sodium fluoride held in the reaction vessel.

Data for the three runs, which are given in Table I, show that the total effect of reactions (1) and (2) is to produce more oxygen than oxygen fluoride and that the latter substance appears to be consumed slowly with the consequent production of oxygen. There is good agreement between the calculated and observed hydrogen fluoride values.

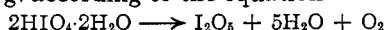
TABLE I

REACTION OF FLUORINE WITH EXCESS PERIODIC ACID			
Sample	I	II	III
Weight of acid, g.	3.08	3.47	3.51
Time of reaction, hr.	1 $\frac{1}{3}$	5	24
Temp., $^\circ\text{C}$.	24.3	23.0	25.2
Vol. of reaction vessel, liters	0.411	0.411	0.411
Initial pressure, cm.	42.0	41.0	40.0
Final pressure, cm.	38.3	28.6	21.8
Millimoles gas entering	9.32	9.10	8.88
Millimoles F_2 consumed	1.64	5.50	8.08
Millimoles OF_2 by analysis	0.22	0.72	0.13
Millimoles O_2 produced	0.60	2.0	3.9
Millimoles HF calculated	2.8	9.6	16
Millimoles HF observed, absorbed by NaF	2.7	9.6	16
% OF_2 by volume, in O_2 - OF_2 , total	27	26	3.2

Although no attempt was made to show the presence of the acid HIO_4 in the product, its existence may be reasonably inferred in the light of

Lamb's¹ work, which showed that the dihydrate was decomposed by dehydration directly to HIO_4 without intermediate compounds. He also found that stronger dehydrating conditions in no instance gave the seven valent anhydride, but rather resulted in decomposition to I_2O_5 .

The second stage in the fluorination was studied by allowing samples of the acid to react in a continuous stream of fluorine at room temperature. The remaining white solid was shown to be iodine pentoxide. It was a non-hygroscopic substance which failed to oxidize manganous ion to permanganate in solution containing sulfuric acid, and its water solution gave a white precipitate with silver ion. During the fluorination of a 2.310-g. sample of $\text{HIO}_4 \cdot 2\text{H}_2\text{O}$, the loss in weight was 0.613 g. This may be compared with the theoretical loss of 0.619 g. according to the equation



Likewise this sample should yield a product with a total oxidation equivalent of 0.0608; the equivalency found iodometrically was 0.0607. Such a change to give iodine pentoxide is in accord with the findings of Lamb.¹

The final stage of the fluorination was accomplished by an increase in temperature to about 250°. On so doing, the iodine pentoxide disappeared while a white solid condensed in a product receiving trap cooled by Dry Ice. This solid was determined to melt at -8° to a colorless liquid which fumed in air. When a weighed sample of this liquid was treated with an acidified solution of potassium iodide and the liberated iodine titrated with standard sodium thiosulfate, an equivalent weight of 36.8 was found. This is in good agreement with the theoretical value of 36.9 for IF_5 (m. p. -8°, b. p. +97°).

The boiling point of the iodine pentafluoride was not determined as the reaction with the glass container was found to be too rapid above 30°. Such a behavior was also reported for IF_5 by Ruff and Braida.²

Acknowledgment.—This work was performed under contract with the Office of Naval Research, U. S. Navy Department.

(1) Arthur B. Lamb, *Am. Chem. J.*, **27**, 134 (1902).

(2) Otto Ruff and A. Braida, *Z. anorg. allgem. Chem.*, **220**, 43-48 (1934).

DEPARTMENT OF CHEMISTRY AND

CHEMICAL ENGINEERING

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The Esterification of Acylated α -Amino Acids

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Esters of the acylated α -amino acids or peptides are ordinarily prepared by the acylation of the α -amino acid or peptide ester or by the traditional acid catalyzed esterification of the acylated α -amino acid or peptide.¹ In seeking a more attrac-

tive procedure than either of the above it has been found that as with other carboxylic acids^{2,3} certain of the acylated α -amino acids may be readily esterified by simply heating an alcoholic solution of the acid at approximately 180° in the absence of added catalyst. While this procedure appears to be useful for the esterification of many acylated α -amino acids it is to be anticipated that a number of acids will form products other than esters. For example with benzoyl-L-arginine the principal reaction product proved to be racemic 5-benzamido-piperidone-2.

Aside from convenience of the above method for the preparation of esters of acylated α -amino acids and carboxylic acids in general³ it is one of the few procedures that can be used for the esterification of ketals of polyhydroxy acids such as 1;2,3;4-diisopropylidene-D-galacturonic acid.⁴

Experimental

Methyl Hippurate.—A solution of 18.0 g. of hippuric acid in 200 ml. of methanol under an initial pressure, at 25°, of 1000 lb./sq. in. of hydrogen was heated at 180-185° for ten hours. The reaction mixture was evaporated to dryness, the residue extracted with ether, the ethereal extract evaporated to dryness and the residue recrystallized from benzene to give 15.9 g. (82.5%) of methyl hippurate, m. p. 81-82°, uncor.

Benzoyl-DL-alanine Methyl Ester.—Benzoyl-DL-alanine (19.3 g.) in 200 ml. of methanol was heated at 180° for twelve hours. The reaction mixture was fractionally distilled and the distillate, b. p. 129-131° (0.15 mm.) was recrystallized from benzene to give 16.9 g. (91%) of benzoyl-DL-alanine methyl ester, m. p. 80-82°, uncor.

Carbobenzoxyl-DL-alanine Methyl Ester.—A solution of 22.3 g. of carbobenzoxyl-DL-alanine in 200 ml. of methanol heated at 180° for twelve hours was fractionally distilled and the fraction, b. p. 129-131° (0.2 mm.), recrystallized from ligroin to give 13.3 g. (59%) of carbobenzoxyl-DL-alanine methyl ester, m. p. 49-50°, uncor.

Anal. Calcd. for $\text{C}_{12}\text{H}_{15}\text{O}_4\text{N}$: C, 60.8; H, 6.3; N, 5.9. Found: C, 61.0; H, 6.5; N, 5.6.

Attempted Esterification of α -Benzoyl-L-arginine.— α -Benzoyl-L-arginine (27.6 g.) in 200 ml. of methanol was heated at 170° for fifteen hours, the reaction mixture filtered (ppt. 7.0 g.), the filtrate evaporated to dryness and the residue recrystallized from hot water to give 8.5 g. (39%) of 5-benzamido-piperidone-2, m. p. 183-184°, insoluble in aqueous acid and alkali, soluble in hot water and ethanol.

Anal. Calcd. for $\text{C}_{12}\text{H}_{14}\text{O}_3\text{N}_2$: C, 66.1; H, 6.4; N, 12.8. Found: C, 66.4; H, 6.7; N, 12.5. The benzamidopiperidone was hydrolyzed with 20% hydrochloric acid and the dipicrate of DL-ornithine, m. p. 198-199°, isolated from the hydrolysate. A solution of α -benzoyl-L-nitroarginine in methanol heated at 170° for seventeen hours gave 68% of 5-benzamido-piperidone-2, m. p. 183-184°.

Methyl Benzoate.—Fractional distillation of a solution of 12.2 g. of benzoic acid in 200 ml. of methanol previously heated at 185° for fifteen hours gave 12.2 g. (90%) of methyl benzoate, b. p. 83° (12 mm.).

Methyl Lactate.—A solution of 12.0 g. of freshly distilled lactic acid, b. p. 78° (0.1 mm.), in 250 ml. of methanol heated at 170° for fourteen hours upon fractional distillation gave 9.6 g. (69%) of methyl lactate, b. p. 143-145°.

(2) W. J. Hickinbottom, "Reactions of Organic Compounds," 2nd ed., Longmans, London, 1948, p. 100.

(3) Private communication from Prof. Homer Adkins, University of Wisconsin, Madison.

(4) C. Niemann, unpublished data.

(1) E. Fischer, "Untersuchungen über Aminosäuren, Polypeptide und Protein," Julius Springer, Berlin (1906, 1923).