was established by analyzing a representative group of samples issued by the National Bureau of Standards. The results are recorded in Table II.

Discussion of Results

The data in Table II show that the reagent may be used successfully for the determination of small amounts of iron in various materials. All values determined with the new reagent are well within the range of values reported by the Bureau. The precision between individual analyses is excellent. Feldspar 70, dolomite 88, silica brick 102 and soda lime glass 128 contained, respectively, 0.012, 0.003, 0.025 and 0.01% of P_2O_5. No interference from phosphate was encountered with any of these samples. When no interfering ions are present, a sodium carbonate fusion of the sample may be taken up in dilute hydrochloric acid, filtered directly into a 100-ml. volumetric flask, diluted to the mark and mixed. An aliquot part of the solution is taken for analysis. Dehydration of the silica before filtration is not necessary.

Summary

A new, sensitive and practically specific reagent for the colorimetric determination of iron is presented. The nature of the reaction and the optimum conditions for color formation have been determined spectrophotometrically. The colored complex obeys Beer's law over the useful range of iron concentration.

The reagent is sensitive to 1 part of iron in 40 million parts of solution when observations are made in Nessler cylinders (50-ml. tall-form). An analytical procedure based on visual methods of color matching has been applied to a variety of materials with good accuracy. The number of interfering cations is small. Iron may be determined in the presence of titanium without interference.

CHARLOTTESVILLE, VA. RECEIVED JULY 31, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

The Effect of Fluorine Substitution on Chemotherapeutic Agents. I. Synthesis of Some Fluorine-Containing Medicinals[1]

BY H. LEON BRADLOW[2] AND CALVIN A. VANDERWERF

Because of the increasing interest in organic compounds containing fluorine we have undertaken a program involving the synthesis of a variety of fluorine substituted compounds, with the ultimate aim of determining the effect on the pharmacological properties of various medicinals produced by the substitution of fluorine atoms for other groups in the molecule. The present paper describes the synthesis of sample compounds of a number of types, the pharmacological and germicidal testing of which it is hoped will provide leads for future work. Previous investigations of this nature have been concerned mainly with the substitution of fluorine for other halogen atoms[3]; in view of the fact that a number of isosteres of important medicinal agents have proved to be as effective or better than the original drugs,[4] however, emphasis in the present work has been placed upon the substitution of fluorine atoms for the isosteric amino and hydroxy groups.[5] Representative fluorine-containing compounds related to medicinals of the following general types were prepared: (1) antimalarials, (2) arsenicals, (3) diphenylsulfones, (4) antiseptics derived from resorcinol and (5) sulfonanilides.

Experimental[6,7]

p-**Nitrofluorobenzene.**—Direct nitration of fluorobenzene by dropwise addition, with vigorous stirring, of 3 moles to 600 cc. of a 2:1 (by volume) mixture of concentrated sulfuric acid and yellow fuming nitric acid (sp. g. 1.5) at −10°, followed by addition of ice, ether extraction and careful fractionation through a packed column of the residue after removal of the ether, gave 338 g. (80%) of *p*-nitrofluorobenzene, b. p. 109–109.5° at 36 mm., f. p. from cooling curve 26.0°, together with 40.0 g. (7.2%) of 2,4-dinitrofluorobenzene, b. p. 129–130° at 2.7 mm. In an alternate method *p*-nitrofluorobenzene was obtained from *p*-nitroaniline in 65% yield by diazotization followed by decomposition at 40° in anhydrous hydrogen fluoride.

p-**Fluoroaniline.**—Reduction of *p*-nitrofluorobenzene in absolute alcohol using Raney nickel catalyst with a small amount of platinum tetrachloride as promoter repeatedly gave 92–95% yields of *p*-fluoroaniline, b. p. 98–99° at 33 mm. With Adams catalyst the reduction in either absolute alcohol or acetic acid gave only 65–70% yields of the amine together with 5% of *p*-fluoroacetanilide, m. p. 150.6–151.1°, when the latter solvent was used; this

(1) Presented before the Organic Division of the American Chemical Society at the Atlantic City meeting in April, 1947.

(2) H. P. Cady Fellow, 1946.

(3) See, for example: (a) Dunker and Starkey, THIS JOURNAL, **61**, 3005 (1939); (b) Suter and Weston, *ibid.*, **61**, 2317 (1939); (c) **62**, 604 (1940); (d) Suter, Lawson and Smith, *ibid.*, **61**, 161 (1939); (e) English, Mead and Niemann, *ibid.*, **62**, 350 (1940).

(4) Compare the bactericidal action of sulfathiazole and of sulfadiazine with that of sulfapyridine, the analeptic activity of the N,N-diethylamide of thiazole-5-carboxylic acid with that of the corresponding derivative of pyridine and the hypnotic properties of dialkyl derivatives of 2,4-dioxothiazolidine with those of the analogous barbiturates.

(5) Relatively few studies of this type have been made; see: (a) Schiemann and Winkelmüller, *Ber.*, **65B** 1435 (1932); (b) Hansen, THIS JOURNAL, **59**, 280 (1937); (c) Fosdick and Campaigne, *ibid.*, **63**, 974 (1941).

(6) All melting points corrected; boiling points uncorrected.

(7) All analyses by Oakwood Laboratories, Alexandria, Virginia.

last-named product was obtained in 77% yield when the reduction was carried out in acetic anhydride.

The low yields (30–35%) of *p*-fluoroaniline consistently obtained from *p*-aminoacetanilide by the Schiemann reaction, followed by hydrolysis of the resulting *p*-fluoroacetanilide, were not improved by the use of the modification[8] in which the borofluoride is added gradually to xylene at 140°.

2-Carboxy-5-chloro-4'-fluorodiphenylamine.—In a modification of the general method of Magidson[9] a mixture consisting of 16.7 g. (0.15 mole) of *p*-fluoraniline, 26.1 g. (0.13 mole) of 2,4-dichlorobenzoic acid, 24 g. of potassium carbonate, 10.1 g. of potassium acetate, 0.15 g. of copper powder and 180 ml. of *n*-butyl alcohol was refluxed for four hours, then steam distilled. The product was isolated in the usual manner[10] and 24–25 g. (90–94%) of reprecipitated material, m. p. 204–209°, was obtained. It crystallized from glacial acetic acid as long yellow needles, m. p. 212.0–213.1°.[11]

Anal. Calcd. for $C_{13}H_9O_2NClF$: N, 5.3; Cl, 13.4. Found: N, 5.4, 5.4; Cl, 13.8, 13.8.

The procedure of Price and Roberts[11] gave the desired product in very poor yield and that of Bachman[10] in 70–75% yields.

2-Fluoro-6,9-dichloroacridine.—Exactly 5.0 g. of 2-carboxy-5-chloro-4'-fluorodiphenylamine was refluxed for four hours with 35.0 g. of phosphorus oxychloride. The latter compound was then partially removed at the water pump and the residue poured into water and chloroform. The chloroform layer was washed with cold water, dried over drierite, and the solvent removed at the pump. After trituration of the black residue with acetone to remove the dark color 2.5 g. (50%) of the desired product was obtained. Because of its obvious instability it was not further characterized.

2-Fluoro-6-chloro-9-(1-methyl-4-diethylaminobutyl)-aminoacridine.—The total product obtained as described above was dissolved in 10 cc. of phenol and 1.5 g. of 1-diethylamino-4-aminopentane was added. After the mixture had been heated on the steam-bath for two hours with stirring the product was isolated in the usual manner as the dihydrochloride. One recrystallization from alcohol–ether gave 2.75 g. (63%) of fine yellow crystals, m. p. 225.0–226.5°, with darkening at 219°.

Anal. Calcd. for $C_{22}H_{29}N_3Cl_3F$: N, 9.1; Cl, 23.0. Found: N, 8.9, 8.9; Cl, 22.7, 22.6.

4-Fluoro-3-nitroaniline.—The procedure of Holleman[12] was modified as follows: 13.8 cc. of yellow fuming nitric acid (sp. g. 1.5) in 72 cc. of concentrated sulfuric acid was added dropwise with stirring at −5° (internal cooling with Dry Ice) to a solution of 33.3 g. (0.3 mole) of *p*-fluoroaniline in 175 cc. of concentrated sulfuric acid. After being stirred at −5° for one hour the mixture was allowed to come to 0° over the course of an additional hour, then poured onto ice, neutralized with sodium carbonate and filtered. Washed with water and dried, the product (36 g., 77%) was obtained as red plates, m. p., after one recrystallization from water, 97.0–98.2°.

4-Fluoro-3-nitrophenylarsonic Acid.—This product, obtained as yellow plates in 49% yield from 4-fluoro-3-nitroaniline by the general method of Doak,[13] darkened at 260° and melted at 279.2–281.3° after recrystallization from hot water.

An alternate sequence *via* the nitration of *p*-fluorophenylarsonic acid was abandoned because of our failure to obtain the acid by any of three plausible methods.[13,14]

3,3'-Diamino-4,4'-difluoroarsenobenzene.—Prepared by the general procedure of Ehrlich and Bertheim,[15] this compound was obtained in 73% yield. It was purified as the dihydrochloride, m. p. 195.2–196.4°, from methyl alcohol–ether. Both compounds are extremely sensitive to oxygen, and satisfactory analyses were not obtained.

3-Amino-4-fluorophenylarsonic Acid.—This compound was obtained in 53% yield by the general method of Stevinson and Hamilton.[16] The procedure of Jacobs[17] gave less satisfactory results.

Because of the extreme air-sensitiveness of the free amine, it was converted directly to the acetyl derivative by treatment of the water solution with acetic anhydride under the Schotten–Baumann conditions. The 3-acetylamino-4-fluorophenylarsonic acid was isolated as brown needles melting at 217.1–218.2° after recrystallization from ethyl alcohol–water.

Anal. Calcd. for $C_8H_9O_4NFAs$: N, 5.1. Found: N, 5.2, 5.0.

***p*-Amino-*p'*-fluorodiphenylsulfone.**[18]—To a solution of 13.8 g. of *p*-amino-*p'*-nitrodiphenylsulfone[19] in 35 cc. of concentrated hydrochloric acid and 60 cc. of water, 3.5 g. of sodium nitrite dissolved in 25 cc. of water was added rapidly. After the mixture had been stirred for twenty minutes 17.0 g. of sodium fluoborate in a minimum of water was added and stirring was continued for an additional forty-five minutes. A quantitative amount (18.4 g.) of the borofluoride was isolated in the usual manner.

In a typical decomposition, a small flask containing 8.1 g. of the borofluoride was immersed in an oil-bath heated to 145° until evolution of boron trifluoride ceased. The black product was extracted with benzene, the combined extracts filtered and the filtrate concentrated to give 4.1 g. (63%) of fine crystals. These were reduced[20] directly to yield 2.6 g. (70%) of *p*-amino-*p'*-fluorodiphenylsulfone, m. p., after recrystallization from alcohol–water, 200.4–201.6°.

Anal. Calcd. for $C_{12}H_{10}O_2NSF$: S, 12.8; N, 5.6. Found: S, 12.6, 12.7; N, 5.8, 5.9.

***p*-Fluorobenzenesulfonyl Chloride.**—The procedure of Huntress[21] was found to be satisfactory on a large scale if the reaction was conducted at −5 to 0° with vigorous stirring and the reaction mixture was then allowed to stand overnight. The product, purified by distillation at 105–110° at 5 mm., was isolated in 83% yield. The amount of sulfone formed was negligible.

***p*-Chloro-*p'*-fluorodiphenylsulfone.**—This compound was prepared in 69% yield by the procedure of Beckurts,[22] modified in that the reaction mixture after hydrolysis was steam distilled to remove excess chlorobenzene. Recrystallized from alcohol–water, it formed large prisms melting at 113.2–113.6°.

Anal. Calcd. for $C_{12}H_8O_2SClF$: S, 11.9. Found: S, 12.1, 12.1.

***p*-Fluoro-*p'*-hydroxydiphenylsulfone.**—The methoxy derivative was prepared in 90% yield by the method of Beckurts[22] with the modification described above. It melted at 88.5–90.1° after recrystallization from alcohol–water.

(8) Zenitz and Hartung, *J. Org. Chem.*, **11**, 444 (1946).

(9) Magidson, Grigorovskii and Gal'perin, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 56 (1938).

(10) Bachman and Wetzel, *J. Org. Chem.*, **11**, 454 (1946).

(11) Price and Roberts, *ibid.*, **11**, 463 (1946).

(12) Holleman, *Rec. trav. chim.*, **23**, 225 (1904).

(13) Doak, THIS JOURNAL, **62**, 167 (1940).

(14) (a) Ruddy, Starkey and Hartung, *ibid.*, **64**, 828 (1942); (b) Palmer with Adams, *ibid.*, **44**, 1356 (1922).

(15) Ehrlich and Bertheim, *Ber.*, **45**, 756 (1912).

(16) Stevinson and Hamilton, THIS JOURNAL, **57**, 1298 (1935).

(17) Jacobs, Heidelberger and Rolf, *ibid.*, **40**, 1580 (1918).

(18) The obvious method for the preparation of this compound by way of *p*-amino-*p'*-nitrodiphenyl sulfide was attempted but abandoned because of our failure, despite repeated attempts, to obtain the latter compound by the procedure of Raiziss, *et al.*, *ibid.*, **61**, 2763 (1939).

(19) Obtained by the hydrolysis of *p*-nitro-*p'*-acetylaminodiphenylsulfone ["Organic Syntheses," Vol. 22, 31 (1942)] with hydrochloric acid in alcohol solution.

(20) According to method of Ferry, Buck and Baltzly, ref. cited under (19).

(21) Huntress and Carten, THIS JOURNAL, **62**, 511 (1940).

(22) Beckurts and Otto, *Ber.*, **11**, 2066 (1878).

Anal. Calcd. for $C_{13}H_{11}O_3SF$: S, 12.1. Found: S, 12.2, 12.4.

The desired hydroxy compound was prepared by refluxing 10.0 g. of the methoxy derivative in a mixture of 100 cc. of acetic acid and 125 cc. of concentrated hydrobromic acid for sixty hours. The reaction mixture was diluted with water, made almost neutral with sodium hydroxide, and the product extracted with benzene which was then back-extracted with 20% sodium hydroxide solution. The latter solution was re-acidified and extracted with benzene. After washing with water and drying the solvent was evaporated leaving 7.0 g. (74%) of *p*-fluoro-*p'*-hydroxydiphenylsulfone, m. p. 111.8–113.1°, following recrystallization from alcohol–water.

Anal. Calcd. for $C_{12}H_9O_3SF$: S, 12.7. Found: S, 12.9, 12.9.

p,p'-Difluorodiphenylsulfone.—Because of the facts that the application of the generalized Schiemann procedure in the case of *p,p'*-diaminodiphenylsulfone led only to the formation of tarry material and that the results of Huntress[21] could not be duplicated[23] the conventional method of Beckurts[22] was employed. The compound, m. p. 97.5–98.1°,[24] even after repeated recrystallization from alcohol, was obtained in 95% yield.

Anal. Calcd. for $C_{12}H_8O_2SF_2$: S, 12.6. Found: S, 12.5, 12.5.

***m*-Fluorophenol.**—Approximately 580 g. (29 moles) of anhydrous hydrogen fluoride was added to 163 g. (1.5 moles) of *m*-aminophenol contained in a 1-liter copper beaker cooled in ice. To the stirred mixture 104 g. (1.5 moles) of sodium nitrite was added over the course of one hour; stirring was continued for two more hours. The reaction mixture was then allowed to stand for two days in an iron flask provided with an efficient hydrogen fluoride condenser, after which it was steam distilled and the distillate extracted with ether. After the ether extract had been washed with ammonium hydroxide and dried, the solvent was removed and the residue distilled to yield 58.2 g. (35%)[25] of *m*-fluorophenol, b. p. 97–103° at 46 mm.

An alternate method of synthesis using the Schiemann reaction was attempted unsuccessfully. Preparation of *m*-nitroanisole by the procedure of Vermeulen[26] was effected in quantitative yields provided that carefully purified *m*-nitrophenol was used. The *m*-nitroanisole was reduced to *m*-anisidine in 82% yield with Raney nickel catalyst in absolute alcohol. The borofluoride of the latter compound, however, decomposed spontaneously at room temperature.

2-Acetoxymercuri-5-fluorophenol.[27]—To a solution of 3.9 g. of *m*-fluorophenol in 60 cc. of water was added 10.8 g. of mercuric acetate in 30 cc. of water acidulated with acetic acid. After four days of standing the mixture was filtered and the precipitate washed with water, dried and recrystallized from acetic acid. The product (10.4 g., 80%) crystallized as colorless plates, decomposing over a wide range starting at 250°.

The *s*-Amyl-5-fluorophenols.—Application of the method of Klarman, *et al.*,[28] to *m*-fluorophenol gave two isomers, the first boiling at 88–91° at 1.5 mm., and the second at 93–95° at 0.4 mm. No attempt was made to determine the exact structure of these compounds, which are probably 2-*s*-amyl-5-fluorophenol and 4-*s*-amyl-5-fluorophenol.

Anal. Calcd. for $C_{11}H_{15}OF$: C, 72.5; H, 8.2. Found for first isomer: C, 72.3, 72.7; H, 8.0, 8.1. Found for second isomer: C, 72.1, 72.4; H, 8.1, 8.1.

3,3-bis-(4-Fluorophenyl)-phthalide.—To a mixture of 8.0 g. of phthaloyl chloride and 40 cc. of fluorobenzene kept at 60–70° anhydrous aluminum chloride (7.6 g.) was added in small portions with shaking. The mixture was warmed on a steam-bath for three hours and then allowed to stand at room temperature overnight. Following removal of the fluorobenzene at the water pump the residue was stirred with dilute sodium hydroxide solution for several hours and the mixture was then acidified to yield 12.0 g. (92%) of the phthalide, m. p., after recrystallization from alcohol–water, 125.1–126.2°.

Anal. Calcd. for $C_{20}H_{12}O_2F_2$: C, 74.5; H, 3.7. Found: C, 74.4, 74.4; H, 3.9, 3.8.

Attempted condensation of fluorobenzene and phthalic anhydride in the presence of sulfuric acid or anhydrous hydrogen fluoride under a variety of conditions was unsuccessful.

N⁴-Acetyl-*p'*-fluorosulfanilanilide.—Exactly 13.0 g. of acetylsulfanilyl chloride was added gradually to a solution of 5.6 g. of *p*-fluoroaniline in 34 cc. of acetone and 5 cc. of pyridine. After standing overnight the mixture was filtered, the filtrate concentrated, 50 cc. of water added with stirring and the mixture filtered to yield 9.8 g. (63%) of colorless needles, m. p. 189.9–190.1°, after recrystallization from alcohol–water.

Anal. Calcd. for $C_{14}H_{13}O_3N_2SF$: N, 9.1; S, 10.4. Found: N, 9.1, 9.1; S, 10.6, 10.7.

Hydrolysis of the acetyl compound gave a 94% yield of *p'*-fluorosulfanilanilide, m. p. 163.2–164.1°[29] after recrystallization from alcohol–water.

N⁴-Succinyl-*p'*-fluorosulfanilanilide.—Prepared in 92% yield by the general procedure of Miller, *et al.*,[30] this product melted at 141.3–142.9° after recrystallization from alcohol–water.

Anal. Calcd. for $C_{16}H_{15}O_5N_2SF$: S, 8.8; N, 7.7. Found: S, 8.3, 8.4; N, 7.9, 8.0.

4'-Fluoro-4-succinimido-benzenesulfonanilide.—This compound was prepared in 61% yield by the general method of Miller, *et al.*[30] It formed micro-crystals from hot water, m. p. 156.1–157.5°.

Anal. Calcd. for $C_{16}H_{13}O_4N_2SF$: S, 9.2; N, 8.1. Found: S, 9.2, 8.9; N, 8.0, 8.0.

Acknowledgment.—We wish to acknowledge the kindness of Dr. C. M. Suter of the Winthrop Research Institute for supplying the noval diamine and to Parke, Davis and Company for supplying the *p,p'*-diaminodiphenylsulfone used in this investigation.

Summary

As the preliminary step in a study designed to determine the effect of fluorine substitution on chemotherapeutic and germicidal agents a number of new fluorine-containing compounds related to medicinals of the following general types have been prepared and described: (1) antimalarials, (2) arsenicals, (3) diphenylsulfones, (4) antiseptics derived from resorcinol and (5) sulfonanilides. Specifically, synthesis of the following compounds has been described: 2-fluoro-6-chloro-9-(1-methyl-4-diethylaminobutyl)-aminoacridine as an

(23) Despite repeated attempts, the only product obtained by the direct action of chlorosulfonic acid on fluorobenzene, even when more drastic conditions were employed, was *p*-fluorobenzenesulfonyl chloride. The reported formation of *p,p'*-difluorodiphenylsulfone may, perhaps, be due to the unsuspected presence in the reaction mixture of small amounts of some catalytic agent.

(24) Huntress and Carten, ref. 21, reported 100°.

(25) Although the yield is low, this procedure has the advantages of simplicity and ready availability of the starting material, *m*-aminophenol.

(26) Vermeulen, *Rec. trav. chim.*, **25**, 12 (1906).

(27) Although the exact structure of the compound has not been proved, the assigned structure appears likely on the basis of the strong *para*-orienting effect of the fluorine atom.

(28) Klarman, Shternov and Gates, THIS JOURNAL, **55**, 2576 (1933).

(29) In agreement with value reported by Suter and Weston, ref. 3c.

(30) Miller, Rock and Moore, THIS JOURNAL, **61**, 1198 (1939).

analog of atebrin; 3,3′-diamino-4,4′-difluoroarsenobenzene, 3-amino-4-fluorophenylarsonic acid and 3-acetylamino-4-fluorophenylarsonic acid as analogs of the trypanocidal 3-amino-4-hydroxy-compounds; *p*-amino-*p*′-fluorodiphenylsulfone, *p*-chloro-*p*′-fluorodiphenylsulfone, *p*-fluoro-*p*′-hydroxydiphenylsulfone and *p*,*p*′-difluorodiphenylsulfone as analogs of diphenylsulfones of current interest; 2-acetoxymercuri-5-fluorophenol and two isomeric *s*-amyl-5-fluorophenols as analogs of the germicidal resorcinol derivatives; 3,3-bis-(4-fluorophenyl)-phthalide as an analog of phenolphthalein; and *p*-fluoro- derivatives of N^4-succinylsulfanilanilide and 4-succinimido-benzenesulfonanilide.]

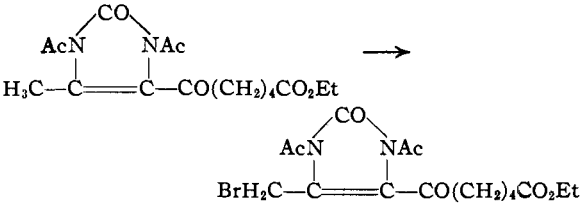
LAWRENCE, KANSAS RECEIVED AUGUST 23, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

Synthesis of Imidazolones Structurally Related to Biotin by Means of N-Bromosuccinimide[1]

BY ROBERT DUSCHINSKY AND L. ALLEN DOLAN

The preparation of 1,3-diacetyl-4-bromomethyl-5-(δ-carbethoxyvaleryl)-2-imidazolone as illustrated



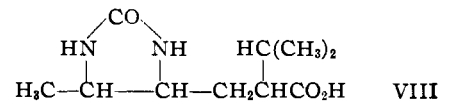
by application of Ziegler's[2] bromination method and the replacement of the bromine by oxygen-containing groups were essential steps in a recently reported synthesis of O-heterobiotin.[3]

The present paper demonstrates the versatility of the bromination and replacement reactions in the synthesis of a number of imidazolone derivatives. Some of them are structurally related to biotin since they possess its C,N skeleton and carry in the α-position of the side chains heteroatom-containing groups. The bromo compounds and substitution products are listed in Table I. Starting materials are the corresponding bromine-free compounds.

With the exception of 4-methyl-5-carbethoxy-2-imidazolone, which directly reacted with bromine to give I, diacylated imidazolones were used for the bromination by Ziegler's method.[4] The bromination was achieved by refluxing a carbon tetrachloride solution of such an imidazolone with one or, for the preparation of the dibromo compound IV, with two moles N-bromosuccinimide until the latter was completely converted into succinimide. The bromo compounds obtained in good yields are crystalline, not lachrymatory solids, which are sometimes inclined to undergo decomposition with release of hydrobromic and acetic acid. It is, therefore, advantageous to proceed at once with the desired replacement reaction. Depending on the reagent and reaction conditions, the replacement of the bromine may be accompanied by total or partial loss of the acetyl groups. Formation of mixtures of unacetylated, mono- and diacetylated products explains some of the low yields encountered in the substitution reactions.

Proof of the introduction of bromine into the methyl group has been established for the keto ester VI.[3] The same is true for compound I, because it was found to be identical with the product obtained from ethyl δ-ethoxy-β-ketobutyrate via 4-ethoxymethyl-5-carbethoxy-2-imidazolone (IA).[5]

The structure of III was established by conversion into an acetyl-free substitution and hydrogenation product. Thus, application of a method described for the preparation of 5-allyl-5-isopropylbarbituric acid[6] gave the barbiturate IIIA in fair yield. Due to its "de-aromatization" by acetyl groups,[3] the compound could be hydrogenated with palladium charcoal catalyst at room temperature, whereby only one of the two possible diastereomers, undoubtedly the *cis* form, was obtained in excellent yield.[7] It was readily deacetylated by cold sodium hydroxide. The obtained 4-methyl-5-(5′-isopropyl-5′-barbituryl-methyl)-2-imidazolidone was microbiologically inactive. Attempts to cleave the barbiturylimidazolone and imidazolidone for the purpose of obtaining the desthiobiotin isomer VIII correspond-



VIII

(1) Presented before the Division of Organic Chemistry, 109th Meeting of the American Chemical Society, Atlantic City, New Jersey, April 10, 1946.

(2) Ziegler, Späth, Schaaf, Schumann and Winkelmann, *Ann.*, **551**, 80 (1942).

(3) Duschinsky and Dolan, "Jubilee Vol. Emil Barell," Basle, 146 (1946).

(4) 1,3-Diacetyl-4,5-dimethyl-2-imidazolone reacted also with bromine to give the dibromo derivative IV, but the yield was very low.

(5) Duschinsky and Dolan, THIS JOURNAL, **68**, 2350 (1946).

(6) Hoffmann-La Roche and Co., German Patent 526,854 (1930); *C. A.*, **25**, 4893 (1931).

(7) The barbiturate IIIA and its hydrogenation product were found devoid of hypnotic properties by Dr. G. Lehmann of the Pharmacological Laboratories of Hoffmann-La Roche Inc.