Experimental Details[6]

General Procedure.—Sulfanilyl-methylisothiourea (0.01 mole) and the appropriate amine (0.03 mole) were mixed with water (4 cc.), whereupon usually an exothermic reaction set in and methyl mercaptan was evolved. After standing at room temperature for twenty-four hours, the mixture was heated on a water-bath for one hour. On cooling, the reaction product crystallizes in almost quantitative yield (see Table I). Three of the products are new compounds.

From Table I, it can be seen that in contrast to the homologous series of the isothiourea derivatives,[3] the butyl- and benzyl-sulfaguanidine derivatives show much higher melting points, than would be expected from comparison with the isothiourea derivatives.

N^4-Carbethoxysulfanilamide (V).—N^4-Carbethoxysulfanilylthiourea[3] (1 g.) and 10 cc. of a 15% solution of ammonia in ethanol were heated in a sealed tube for four hours at 150°. On cooling, the reaction product crystallized spontaneously. After two crystallizations from butanol, the substance was obtained as twinned leaflets, m. p. 235–236°; mixed m. p. with N^4-carbethoxysulfanilamide,[4] was 236°. *Anal.* Calcd. for $C_9H_{12}O_4N_2S$: C, 44.3; H, 4.9. Found: C, 44.2; H, 5.1.

(6) With the assistance of Z. Weinberg.

Summary

Aminolysis of sulfanilylalkylisothioureas gives excellent yields of alkylated sulfaguanidines by replacement of the alkylthio group. Three new members of the series have been prepared. Ammonolysis of the isothiourea derivatives, on the other hand, was unsuccessful, and N^4-carbethoxysulfanilyl-A, butylisothiourea was attacked neither on the isothiourea group nor on the ethoxyl by ammonia. N^4-Carbethoxysulfathiourea is split by ammonia to N^4-carbethoxysulfanilamide.

REHOVOTH, PALESTINE RECEIVED MARCH 15, 1945

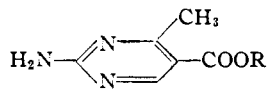
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

An Isomer of Thiamin[1]

BY CHARLES C. PRICE,[2] NELSON J. LEONARD AND ROBERT H. REITSEMA

In order to define further the limits of variation in structure of thiamin type compounds which would permit retention of antineuritic activity, an isomer of thiamin has been prepared in which the positions of the amino and methyl groups on the pyrimidine ring are reversed.

Syntheses of the requisite 2-amino-4-methyl-5-aminomethyl- or halomethylpyrimidine were suggested by the numerous preparations of the pyrimidine portion of thiamin itself. Two of these methods,[3,4] used to produce properly-substituted pyrimidines directly by ring closure, did not appear feasible due to the difficulty of obtaining the necessary dicarbonyl compound. Another approach to the preparation of the desired pyrimidine had been conversion of the ester group of a 5-carbethoxypyrimidine to the nitrile by dehydration of the amide.[5] However, the amide of the readily available 2-amino-4-methyl-5-carbethoxypyrimidine could not be prepared by ammonolysis of the ester (I).



(I) R = C_2H_5
(II) R = H

Unchanged ester was recovered after five days shaking with concentrated ammonium hydroxide at room temperature or after twelve hours heating at 130° with liquid ammonia. Addition of ammonium chloride as a catalyst[6] was of no avail. Hydrolysis to the acid was the main reaction occurring when I was heated at 150° with concentrated ammonium hydroxide, whereas no reaction was observed after heating the ester at 75° for fifteen hours. Intermediate temperatures were used, but in no instance was the desired amide produced in even moderate amounts. The difficulty of preparing amides of 5-carbethoxypyrimidines possessing an adjacent methyl group was also noted by Grewe.[3]

The ester group of ethyl 2-methyl-4-amino-5-pyrimidinecarboxylate has been converted to an aldehyde group by application of a McFadyen–Stevens reaction.[7] An attempted application of this synthesis failed for the isomeric ester (I) since the necessary intermediate in the reaction, the hydrazide of I, could not be prepared.

Further attempts to convert the ester group of I to a hydroxymethyl group by reduction at high temperature and pressure with a copper chromite catalyst resulted in decomposition of the pyrimidine ring. Electrolytic reduction of the corresponding acid II yielded a resin which could not be purified.

Since conversion of the ester group of I to a useful derivative proved impracticable, the corresponding nitrile (IX) has been prepared by the application of the Rosenmund–von Braun nitrile synthesis to 2-amino-4-methyl-5-bromopyrimidine (VI). The latter was obtained by bromination[8] of 2-amino-4-methylpyrimidine (V). The prepa-

(1) The work described in this paper was done in part under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

(2) Present address: Department of Chemistry, University of Notre Dame, Notre Dame, Indiana.

(3) Grewe, *Z. physiol. Chem.*, **242**, 89 (1936).

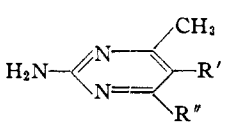
(4) Williams and Cline, THIS JOURNAL, **58**, 1504 (1936).

(5) Todd and Bergel, *J. Chem. Soc.*, 364 (1937).

(6) Fellinger and Audrieth, THIS JOURNAL, **60**, 579 (1938).

(7) Price, May and Pickel, *ibid.*, **62**, 2818 (1940).

(8) Benary, *Ber.*, **63B**, 2601 (1930).



(III) R′ = H, R″ = OH
(IV) R′ = H, R″ = Cl
(V) R′ = H, R″ = H
(VI) R′ = Br, R″ = H
(VII) R′ = Br, R″ = OH
(VIII) R′ = Br, R″ = Cl

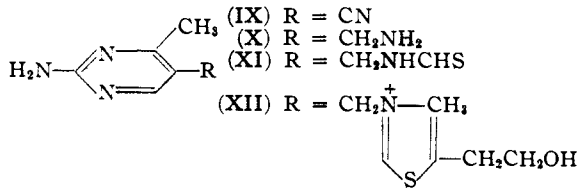
ration of 2-amino-4-methylpyrimidine (V) was accomplished by removal of the chlorine from 2-amino-4-methyl-6-chloropyrimidine (IV) which was in turn prepared from 2-amino-4-methyl-6-hydroxypyrimidine (III).[9] A chemical reduction using zinc dust[9] produced V from the crude chloropyrimidine in 65% yield based on the hydroxypyrimidine. A catalytic reduction by the method described by Backer and Grevenstuk[10] using a palladium–charcoal catalyst in an alcoholic potassium hydroxide solution gave 67% of the theoretical amount of V based on purified chloropyrimidine. The chemical reduction was considered the more convenient laboratory method since larger portions could be used than with the catalytic method and since relatively large amounts of catalyst were necessary in the catalytic method. Another method reported in the literature[8] for the direct synthesis of V from formylacetone and guanidine gave irreproducible yields varying from 10 to 60%.

Bromination of III was attempted as an alternate synthesis of VI especially since its preparation by this method would serve to confirm the position of the bromine atom. The intermediates VII and VIII were obtained in good yields, but the hope that the activation of the chlorine atom due to its position adjacent to the nitrogen would lead to its selective reductive elimination was not realized. Chemical reduction with zinc was ineffective. Catalytic reduction proceeded smoothly but there was no break after one equivalent of hydrogen had been absorbed and the product was a mixture, apparently of the starting material and the three possible dehalogenation products.

Application of the Rosenmund–von Braun nitrile synthesis to 2-amino-4-methyl-5-bromopyrimidine (VI) was successful and in this manner the preparation of the cyanopyrimidine IX was realized. The structure of this intermediate, and consequently of the thiamin isomer, was demonstrated by the alkaline hydrolysis of the nitrile group of IX and the identity of the resulting acid with an authentic sample of II prepared by hydrolysis of the ester (I).

The procedure described by Huber[11] for converting 2,4-diamino-5-cyanopyrimidine to a thiamin analog was applied to the cyanopyrimidine IX. The intermediate pyrimidines, X and XI, were obtained in good yields.

The new isomer of thiamin was bioassayed with rats for thiamin activity employing the curative

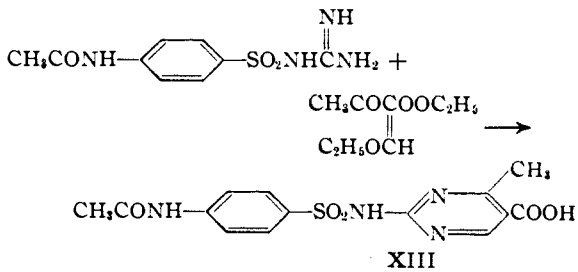


(IX) R = CN
(X) R = CH_2NH_2
(XI) R = CH_2NHCHS
(XII) R = $CH_2\overset{+}{N}=CH_3$ (with $-CH_2CH_2OH$)

method and was found to be devoid of activity.[12]

Incidental to this work, attempts were made to prepare the *p*-aminobenzenesulfonamide derivative of I. Treatment of the ester with *p*-nitrobenzenesulfonyl chloride was not successful at the ordinary temperatures used for such condensations. Other 2-aminopyrimidines bearing negative substituents in the 5-position have shown a similar lack of reactivity.[13,14] Excessive decomposition occurred at the elevated temperatures used by Roblin, Winnek and English.[13]

A satisfactory method for preparing the corresponding acid was found to be the condensation of N^4-acetylsulfanilylguanidine with ethoxymethyleneacetoacetic ester.



XIII

This condensation was carried out under conditions identical to those used for the preparation of the ester (I) from guanidine carbonate and ethoxymethyleneacetoacetic ester. It is of interest to note that hydrolysis of the ester group occurred in this instance. Conversion of XIII to the free amine was readily accomplished by hydrolysis of the acetyl group with aqueous alkali.

Compound XIII, 2-(N^4-acetylsulfanilamido)-4-methyl-5-carboxypyrimidine, SN-7915,[15] was submitted for testing as a potential antimalarial and proved to be inactive.

Experimental[16]

2-Amino-4-methyl-5-carbethoxypyrimidine (I).—The procedure of Mitter and Palit[17] was followed to produce a 74% yield of I, m. p. 220–222°.

Anal. Calcd. for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.20; N, 23.19. Found: C, 53.31; H, 6.16; N, 23.05.

2-Amino-4-methyl-5-carboxypyrimidine (II).—Saponification of I was accomplished by refluxing for one and one-

(9) Gabriel and Colman, *ibid.*, **32**, 2921 (1899).

(10) Backer and Grevenstuk, *Rec. trav. chim.*, **61**, 291 (1942); *C. A.*, **38**, 2326 (1944).

(11) Huber, THIS JOURNAL, **65**, 2222 (1943).

(12) The authors are indebted to Dr. Gladys Emerson of Merck Institute for the results of the pharmacological tests.

(13) Roblin, Winnek and English, THIS JOURNAL, **64**, 567 (1942).

(14) Price, Leonard and Curtin, *J. Org. Chem.*, **10**, 318 (1945).

(15) The Survey Number, designated SN—, is used to identify a compound in the records of the Survey of Antimalarial Drugs. The antimalarial activity of these compounds will be tabulated in a forthcoming monograph.

(16) The microanalyses were carried out by Miss Theta Spoor and Miss Lillian Hruda.

(17) Mitter and Palit, *Quart. J. Indian Chem. Soc.*, **2**, 61 (1925).

half hours 10 g. (0.055 mole) of I in 300 cc. of ethanol containing 3 g. of potassium hydroxide. The solution was cooled and filtered. The solid material was taken up in water and neutralized with dilute acetic acid. After recrystallization from a large volume of water, the acid melted at 313–316° (dec.). Mitter and Palit reported that the compound decomposed at 256–258°.

Anal. Calcd. for $C_6H_7N_3O_2$: C, 47.10; H, 4.51. Found: C, 46.99; H, 4.61.

2-(N^4-Acetylsulfanilamido)-4-methyl-5-carboxypyrimidine (XIII).—To a solution of 10 g. (0.44 mole) of metallic sodium dissolved in 300 cc. of absolute ethanol was added 18.6 g. (0.1 mole) of ethoxymethyleneacetoacetic ester and 25.6 g. (0.1 mole) of N^4-acetylsulfanilylguanidine. The mixture was shaken for twelve hours. The solid was removed by filtration and dissolved in a minimum amount of alkali. All unchanged N^4-acetylsulfanilylguanidine was removed by filtration of the alkaline solution. The clear filtrate was acidified with acetic acid and the precipitate was collected on a filter. The yield of crude product was 25.0 to 28.0 g. (66 to 76%). After one recrystallization from acetic acid and three recrystallizations from ethanol, in which it is very soluble, 2-(N^4-acetylsulfanilamido)-4-methyl-5-carboxypyrimidine melted at 248–249° (dec.).

Anal. Calcd. for $C_{14}H_{14}N_4O_5S$: C, 48.00; H, 4.03; N, 16.00. Found: C, 48.01; H, 4.07; N, 15.77.

2-Sulfanilamido-4-methyl-5-carboxypyrimidine.—A solution of 5 g. (0.014 mole) of 2-(N^4-acetylsulfanilamido)-4-methyl-5-carboxypyrimidine in 14 cc. of water containing 1.4 g. of sodium hydroxide was boiled under reflux for one hour. The solution was clarified by treatment with Darco and just acidified with dilute hydrochloric acid. The light yellow product weighed 4.1 g. It was recrystallized from aqueous ethanol to produce a white solid which melted at 263–264°.

Anal. Calcd. for $C_{12}H_{12}N_4O_4S$: C, 46.78; H, 3.93. Found: C, 46.69; H, 3.96.

2-Amino-4-methyl-5-bromopyrimidine (VI).—This compound was prepared by bromination of 2-amino-4-methylpyrimidine according to the directions of Benary.[6] Recrystallization from dilute acetic acid yielded 70% of VI, m. p. 193–195°.

2-Amino-4-methyl-5-bromo-6-hydroxypyrimidine (VII).—Twenty-five grams (0.2 mole) of 2-amino-4-methyl-6-hydroxypyrimidine was dissolved in 125 cc. of glacial acetic acid at 90° and placed in a 500-cc. three-necked flask fitted with a stirrer, dropping funnel, and a condenser. To the solution was added dropwise with stirring 32 g. (0.2 mole) of bromine over a fifteen-minute period. After the solution had been stirred an additional fifteen minutes it was filtered while still hot. The white precipitate which was obtained in good yields was dissolved in hot water and precipitated by addition of concentrated ammonium hydroxide. After recrystallization from glacial acetic acid soft white crystals were obtained, m. p. 249–250°.

Anal. Calcd. for $C_5H_6BrN_3O$: C, 29.43; H, 2.96; N, 20.60. Found: C, 29.52; H, 2.96; N, 20.43.

2-Amino-4-methyl-5-bromo-6-chloropyrimidine (VIII).—A mixture of 20 g. (0.1 mole) of 2-amino-4-methyl-5-bromo-6-hydroxypyrimidine in 45 cc. of phosphorus oxychloride was boiled under reflux for two hours. The cooled solution was poured onto cracked ice and the suspension was made basic with concentrated ammonium hydroxide. By filtration, 18.5 g. (83%) of light yellow material was isolated. White needles, m. p. 207–208°, were obtained by recrystallization from ethanol.

Anal. Calcd. for $C_5H_5BrClN_3$: C, 26.99; H, 2.28; N, 18.89. Found: C, 27.17; H, 2.39; N, 18.79.

Attempts were made to dehalogenate this material by refluxing in water with zinc dust for six and one-half hours, under conditions which completely dehalogenated 2-phenyl-4-chloro-5-bromopyrimidine,[18] but only starting material was recovered in good yield. A catalytic reduction by the method used successfully to remove the halogen from 2-amino-4-methyl-6-chloropyrimidine showed no break in the curve of the uptake of hydrogen after one equivalent of hydrogen had been absorbed. A mixture of products, m. p. 102–125°, was obtained from a reduction which was stopped after absorption of one equivalent of hydrogen. The separation of the products was not readily accomplished and was abandoned since the preparation of VI as reported in the literature was considered to be superior.

2-Amino-4-methyl-5-cyanopyrimidine (IX).—In a 125-cc. Erlenmeyer flask was placed an intimate mixture of 22.5 g. (0.12 mole) of VI, 15.4 g. (0.17 mole) of cuprous cyanide, 5 cc. of dry pyridine, 5 cc. of dry quinoline, a small crystal of copper sulfate and two drops of benzonitrile (or a trace of IX). The flask was heated in a Wood's metal bath for forty minutes. Two methods were used for isolating the product from the reaction mixture.

(a) The flask was allowed to cool and the contents were chipped loose and ground in a mortar. The powder was washed with ethanol and dried. By a mass sublimation, 7.5 g. (48%) of IX, m. p. 260–264°, was obtained. After recrystallization from ethanol, the nitrile melted at 269–270°.

Anal. Calcd. for $C_6H_6N_4$: C, 53.72; H, 4.59; N, 41.77. Found: C, 53.52; H, 4.44; N, 41.25.

(b) An alternate procedure involved thorough washing of the crude reaction product with 6 *N* ammonium hydroxide followed by washing with water and drying. Ethanol was then used for the continuous extraction of the solid in a Soxhlet apparatus; at least five days was required. By this method, 9.1 g. (57%) of IX, m. p. 249–256°, was isolated.

The use of an additional 5 cc. of pyridine in place of quinoline prevented the formation of IX almost completely. Continued heating of the reaction melt for six hours decreased the yield to 28%. Hydrolysis of IX in an acid medium resulted in decomposition. Basic hydrolysis produced an amphoteric compound, m. p. 308–311° (dec.). This compound did not depress the melting point of 2-amino-4-methyl-5-carboxypyrimidine (II) prepared by saponification of the corresponding ester I.

2-Amino-4-methyl-5-aminomethylpyrimidine (X).—In a bomb containing 50 cc. of methanol and 30 cc. of liquid ammonia was placed 16.3 g. (0.12 mole) of IX. One gram of Raney nickel catalyst was added and the bomb was heated at 120° at an initial pressure of 1000 pounds of hydrogen. The reduction was complete after two hours. To the cooled mixture was added 50 cc. of methanol. The mixture was heated to boiling, and the catalyst was removed by filtration and washed with 20 cc. of methanol. A crop of 7.8 g. of slightly yellow needles crystallized from the cold filtrate. The material was recrystallized from a large volume of petroleum ether (b. p. 90–110°) to produce white needles of **X**, m. p. 152–154°.

Anal. Calcd. for $C_6H_{10}N_4$: C, 52.17; H, 7.30; N, 40.56. Found: C, 52.18; H, 7.14; N, 40.41.

The methanolic filtrate was evaporated to dryness and the residue was dissolved in 20 cc. of water. A slight amount of insoluble material was removed by filtration and 100 cc. of concentrated hydrochloric acid was added to the filtrate. The solution was evaporated under diminished pressure to a volume of about 30 to 50 cc. and 100 cc. of absolute ethanol was added. After the solution had stood in a refrigerator for a few hours, 6.9 g. of the **hydrochloride** of X was obtained. It was recrystallized from dilute ethanol, m. p. 171–172° (dec.).

Anal. Calcd. for $C_6H_{10}N_4 \cdot HCl$: C, 41.26; H, 6.35. Found: C, 41.02; H, 6.39.

The yield of 7.8 g. of **X** and 6.9 g. of its hydrochloride represents 81% of the theoretical amount.

The **dipicrate** was prepared in 95% ethanol solution, m. p. 228–229° (dec.) with slight darkening at 220°.

Anal. Calcd. for $C_{18}H_{16}N_{10}O_{14}$: C, 36.25; H, 2.71; N, 23.49. Found: C, 36.36; H, 2.62; N, 23.73.

(18) Cherbuliez and Stavritch, *Helv. Chim. Acta*, **5**, 267 (1922).

2-Amino-4-methyl-5-thioformamidomethylpyrimidine (XI).—To 1.8 g. (0.01 mole) of the hydrochloride of X dissolved in 5 cc. of water and cooled below 15° a solution of 1.2 g. of potassium carbonate in 4.0 cc. of water was added as rapidly as possible with cooling. A solution of 1.2 g. of potassium dithioformate in 3.5 cc. of water was added immediately and the mixture was stirred for four hours at room temperature. The solid material was isolated by filtration and washed with water. The washed product was dissolved in 8 cc. of 50% acetic acid and filtered from a small amount of insoluble material. The warm solution was neutralized with ammonium hydroxide (sp. gr. 0.89), cooled, and filtered. The dried solid, which had a slightly green cast, weighed 1.3 g. (71%), m. p. 192–198°. After two recrystallizations from water, XI melted at 212–213°.

Anal. Calcd. for $C_7H_{10}N_4S$: C, 46.13; H, 5.53; N, 30.74. Found: C, 46.04; H, 5.76; N, 30.31.

3-(2′-Amino-4′-methyl-5′-pyrimidylmethyl)-4-methyl-5-(2-hydroxyethyl)-thiazolium Bromide Hydrobromide (XII).—With stirring, 6.8 g. (0.037 mole) of XI was added to a solution of 8.62 g. (0.039 mole) of 3-bromo-3-acetopropyl acetate in 15 cc. of anhydrous formic acid warmed to 45°. The temperature was maintained at 45° for two and one-half hours and at 60° for one and one-half hours. The mixture was allowed to stand in a refrigerator overnight. Very little solid had appeared and the mixture was evaporated to dryness under a jet of air. The solid residue was taken up in 20 cc. of 10% aqueous hydrobromic acid and extracted twice with 20-cc. portions of methylene chloride. After stirring twice with Darco at 40° for one-half hour periods the solution was evaporated to a volume of about 7 cc. and 60 cc. of absolute ethanol was added to the warm solution. From the cold solution 1.9 g. of yellow needles, m. p. 190–192° (dec.), were obtained. Recrystallization from a water–ethanol mixture produced white needles which decomposed at 184–185° (dec.).

Anal. Calcd. for $C_{12}H_{16}N_4OS\cdot 2HBr$: C, 33.82; H, 4.26. Found: C, 33.74; H, 4.55.

Summary

An isomer of thiamin, 3-(2′-amino-4′-methyl-5′-pyrimidylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium bromide hydrobromide, has been prepared and was found to be devoid of thiamin activity.

The sulfa derivative of 2-amino-4-methyl-5-carboxypyrimidine has been prepared. The acetyl derivative possessed no antimalarial activity.

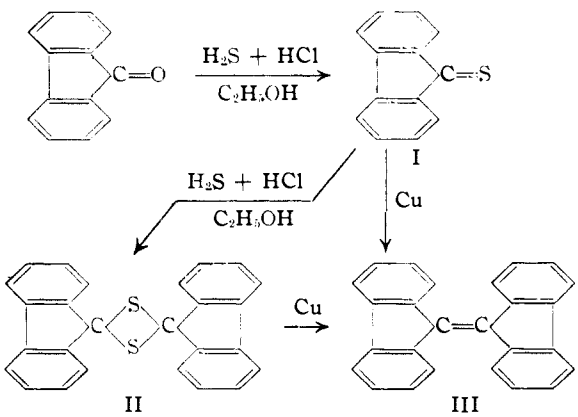
URBANA, ILLINOIS RECEIVED JANUARY 5, 1946

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

Thiocarbonyls. II. Thiofluorenone[1]

BY E. CAMPAIGNE AND WM. BRADLEY REID, JR.[2]

The only known aryl alkyl thione, thioacetophenone, has been obtained in the monomeric form as an unstable purple oil which readily trimerizes.[3] With one notable exception, all of the diaryl thiones have been found to exist in the monomeric form.[4] The exception is thiofluorenone, which has been isolated as the dimer by Bergmann and Hervey,[5] who noted that treatment of a cold alcoholic solution of fluorenone with dry hydrogen chloride and dry hydrogen sulfide for twenty-four hours yielded a yellow precipitate of dithiofluorenone, II.



Smedley[6] attempted to prepare thiofluorenone in several ways, none of which were successful. The action of potassium bisulfide on 9,9-dichlorofluorene yielded a compound which was shown by Bergmann and Hervey[5] to be 9,9′-difluorenyl disulfide. Potassium sulfide and the keto-dichloride yielded bis-diphenylene-ethylene, III, and the action of phosphorus pentasulfide on the ketone gave no identifiable products.

In view of the fact that all other thiones having an aryl group adjacent to the thiocarbonyl group can be obtained in the monomeric form, it would seem probable that monomeric thiofluorenone could be isolated. In the preparation of trithioacetophenone by the action of dry hydrogen sulfide and dry hydrogen chloride on a cold alcoholic solution of acetophenone,[3] the monomeric thione is first deposited as a purple oil, which gradually trimerizes to a white crystalline solid. Dithiofluorenone has been found to be formed by a similar process; by stopping the reaction after three hours the monomeric thiofluorenone (I) has been isolated in green needles, melting at 75–76° on recrystallization from petroleum ether. If the addition of hydrogen sulfide and hydrogen chloride was allowed to continue for fifteen hours, the deep green color of the solution which developed during the first few hours gradually disappeared, and a golden yellow solid was deposited, which proved to be the dimer, II. In addition to analy-

(1) For the first paper of this series, see THIS JOURNAL, **66**, 1136 (1944).

(2) Taken from part of a thesis to be submitted by Wm. Bradley Reid, Jr., in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Indiana University.

(3) Baumann and Fromm, *Ber.*, **28**, 895 (1895).

(4) Campaigne, *Chem. Rev.*, in press.

(5) Bergmann and Hervey, *Ber.*, **62**, 911 (1929).

(6) Smedley, *J. Chem. Soc.*, **87**, 1253 (1905).