ether, the liquid residue was fractionated to give 3 g. (17.4%) of 2-trimethylsilyl-1-methoxynaphthalene.

Cleavage of 1-Trimethylsilyl-2-hydroxynaphthalene (A) Acid Cleavage.—To 0.6 g. (0.0028 mole) of the silane was added 50 ml. of 20% hydrochloric acid and the mixture was refluxed for eight hours. It was then diluted with water and, after cooling, was extracted with ether. The residue from ether was crystallized from water, 0.4 g. (100%), m. p. 120–121°, which was not depressed when mixed with 2-naphthol.

(B) Alkali Cleavage.—A solution of 0.6 g. (0.0028 mole) of the silane in 25 ml. of acetone was added to 50 ml. of 20% aqueous solution of potassium hydroxide and the mixture was refluxed for twelve hours. Acetone was removed by distillation and the solution was acidified with dilute hydrochloric acid. The acidic mixture was extracted with ether. The residue from ether, 0.3 g. (75%), was identified as 2-naphthol by mixed m. p.

Cleavage of 6-Trimethylsilyl-2-hydroxynaphthalene (A).—Five-tenths gram (0.0023 mole) of the silane was added to 50 ml. of 20% hydrochloric acid and the mixture was refluxed for eight hours. It was diluted with water and the mixture was extracted with ether. The residue obtained from ether was extracted with 10 ml. of petroleum ether (b. p. 30–40°) to remove the starting material and the residue was crystallized from dilute methanol. The product, 0.25 g. (76%) melted at 120–121°, which was not depressed when mixed with 2-naphthol.

(B).—When the solution of 1 g. (0.0046 mole) of the silane in 25 ml. of acetone was refluxed with 20% aqueous potassium hydroxide for twelve hours, the silane was unaffected and the starting material, 1 g., was recovered from the basic solution.

Cleavage of 6-Triphenylsilyl-2-hydroxynaphthalene (A).—Dry hydrogen chloride gas was passed into a stirred refluxing solution of 2 g. (0.005 mole) of the silane in 100 ml. of glacial acetic acid for twenty-four hours. The reaction mixture was diluted with 200 ml. of water and filtered. The filtrate was made basic with sodium bicarbonate solution and the resulting mixture was extracted with ether. Removal of ether left a viscous oil, which on crystallization from water gave a product, 0.4 g. (56%) of melting point 120–121°, which was not depressed when mixed with 2-naphthol. The residue, a sticky material, not melting up to 300°, was probably some polymeric compound.

Summary

Several hydroxy- and methoxy-naphthylsilanes have been prepared by the action of chlorosilanes on the corresponding naphthyllithium compounds.

An examination has been made of the cleavage of 1-trimethylsilyl-2-hydroxynaphthalene, 6-trimethylsilyl-2-hydroxynaphthalene, and 6-triphenylsilyl-2-hydroxynaphthalene by acids and by bases. An attempted demethylation of 3-triphenylsilyl-2-methoxynaphthalene by hydriodic acid gave 2-naphthol.

AMES, IOWA RECEIVED FEBRUARY 2, 1950

[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Quinazolines. IX. A Study of an Unusual Reaction of 5-Diazoacetyl-1,3-dimethyl-2,4-quinazolinedione[1]

BY C. H. WANG, T. C. FENG AND BERT E. CHRISTENSEN

In the course of synthesizing certain amino alcohols with a quinazoline nucleus an unusual side reaction as observed, namely, the loss of a methyl substituent upon the conversion of 5-diazoacetyl-1,3-dimethyl-2,4-quinazolinedione to the corresponding bromomethyl ketone.[2] Oxidation of this ketone, followed by decarboxylation of the acid yielded supposedly 1-(or 3)-methyl-2,4-quinazolinedione, whose m. p. 198° does not agree with either the 3-methyl-2,4-quinazolinedione m. p. 234° reported by Abt[3] and Bogert[4] as resulting from cyclization and methylation experiments, respectively, or for the 1-methyl isomer m. p. 265° reported by Sentara Mayeda[5] or 147° m. p. product reported by Abt,[3] resulting from the cyclization of N-methylanthranilamide.

The preparation of the 3-methyl-2,4-quinazolinedione by the method of Abt and the 1-methyl isomer by the method of Sentara Mayeda were confirmed in this Laboratory. However, repeated attempts to prepare the 1-methyl isomer m. p. 147° using two procedures suggested by Abt were unsuccessful. Although this Laboratory obtained a crude cyclization product with a melting point of approximately 147°, this material was easily resolved on basis of acid solubility into two fractions, one melting at 265°, and the other the starting product. From this work it would appear that Abt's cyclization was only partially complete and his product largely starting material contaminated with the 1-methyl-2,4-quinazolinedione, m. p. 265°. This opinion finds additional support in the fact that the m. p. 147° is far out of line for compounds of this type.

In the search for an explanation of this puzzling question (the existence of what appears to be three compounds which are either 1- or 3-methyl substituted 2,4-quinazolinedione) attention turned to the 5-substituted carboxylic acid intermediate to determine if the same anomaly existed among the 1- and 3-methyl-2,4-quinazolinedione-5-carboxylic acids.

Both the 1-methyl-2,4-quinazolinedione-5-carboxylic acid, m. p. 320°, and the 3-methyl isomer, m. p. 332°, were synthesized in this Laboratory by methods which should leave little doubt as to the position of the methyl substituents. The 3-methyl-2,4-quinazolinedione-5-carboxylic acid

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(2) Wang and Christensen, THIS JOURNAL, **71**, 1440 (1949).

(3) Abt, *J. prakt. Chem.*, [2] **39**, 148 (1889).

(4) Bogert and Scatchard, THIS JOURNAL, **41**, 2062 (1919).

(5) Sentara Mayeda, *C. A.*, **11**, 578 (1916).

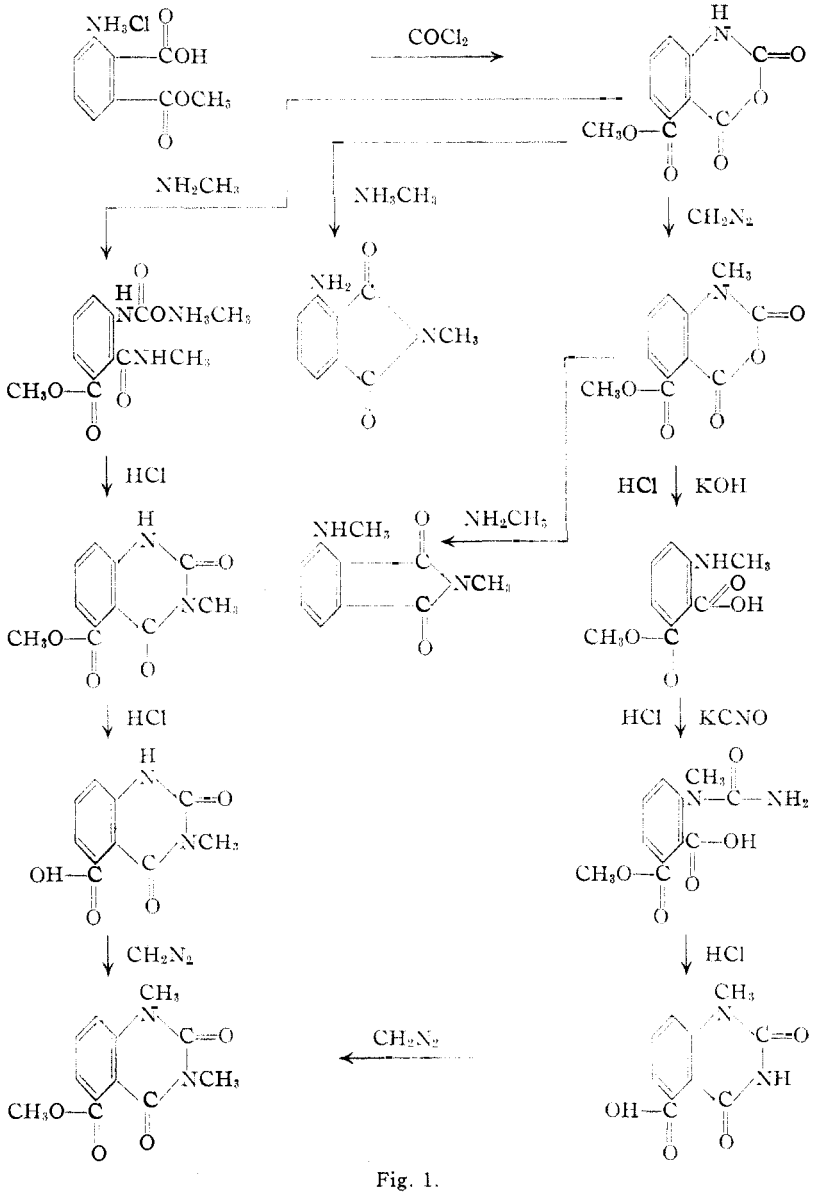

Fig. 1.

was identified as the partial methylation product of 2,4-quinazolinedione-5-carboxylic acid reported earlier by Scott and Cohen[6] as the 1,3-dimethyl derivative but which was later found to be the monomethyl derivative.[2]

Each of these compounds had different melting points which were much higher than the unknown isomeric oxidation product of 5-bromoacetyl-?-methyl-2,4-quinazolinedione. Furthermore, they were stable on melting in contrast to the latter acid which decomposed readily with gas evolution.

Diazomethane methylation of the 1-methyl-(m. p. 320°) and 3-methyl-(m. p. 332°) as well as 2,4-quinazolinedione-5-carboxylic acid gave identical products, the methyl ester of 1,3-dimethyl-2,4-quinazolinedione-5-carboxylic acid, m. p. 144°. This same product was likewise obtained with exhaustive dimethyl sulfate methylation of 2,4-quinazolinedione-5-carboxylic acid (see Fig. 1).

On the other hand, the methylation of ?-methyl-2,4-quinazolinedione-5-carboxylic acid with methyl iodide failed, while diazomethane in an ethereal solution gave the methyl ester. Exhaustive diazomethane methylation in ethereal methanol solution, however, invariably gave a sirupy product from which was isolated a small amount of crystalline material which was isomeric but not identical to methyl-1,3-dimethyl-2,4-quinazolinedione-5-carboxylic acid.

The question of the structure of the original 5-bromoacetyl-?-methyl-2,4-quinazolinedione therefore still remains a mystery. Further experimentation is now underway to approach this interesting problem *via* tracer techniques.

The 1-methyl-2,4-quinazolinedione-5-carboxylic acid was synthesized in a sequence of reactions (see Fig. 1) beginning with 2-amino-6-carbomethoxybenzoic acid hydrochloride. This compound was converted to methyl 2,4-dioxo-3,1,4-benzoxazine-5-carboxylate with phosgene which in turn on methylation with diazomethane gave methyl 1-methyl-2,4-dioxo-3,1,4-benzoxazine-5-carboxylate.

Treatment of the benzoxazine derivative with potassium hydroxide, and then hydrochloric acid gave 6-carbomethoxy-2-methylaminobenzoic acid. This intermediate was cyclized in usual manner with potassium cyanate and hydrochloric acid to 1-methyl-2,4-quinazolinedione-5-carboxylic acid.

The 3-methyl-2,4-quinazolinedione-5-carboxylic acid was likewise synthesized from methyl 2,4-dioxo-3,1,4-benzoxazine-5-carboxylate (see Fig. 1) but by a different sequence of reactions. Ammonolysis of this compound with methylamine gave two products; 6-carbomethoxy-(N-methylammoniumcarboxy) - anthranilic - methylamide which was easily cyclized by hydrochloric acid to methyl 3-methyl-2,4-quinazolinedione-5-carboxylate and 3-amino-N-methylphthalimide. The ester upon further diazomethane methylation

(6) Scott and Cohen, *J. Chem. Soc.*, **119**, 664 (1921).

was identical with the methyl 1,3-dimethyl-2,4-quinazolinedione-5-carboxylate prepared by Wang and Christensen by the diazomethane methylation of 2,4-quinazolinedione-5-carboxylic acid, and by the dimethyl sulfate methylation procedure of Scott[6] and Cohen.

In an attempt to prepare the 1,3-dimethyl-2,4-quinazolinedione-5-carboxylic acid by direct cyclization the methyl 2,4-dioxo-3,1,4-benzoxazine-5-carboxylate was treated with methylamine hydrochloride but instead the desired product gave N-methyl-3-methylaminophthalimide. Concentrated ammonium hydroxide likewise gave the imide 3-methylaminophthalimide. It is evident that the predominant reaction is an ammonolysis of the ester followed by cyclization to the imide rather than direct cyclization to a quinazoline, as is ordinarily the case.

Experimental[7]

Methyl 2,4-Dioxo-3,1,4-benzoxazine-5-carboxylate.—A slow stream of phosgene was introduced through a sintered glass gas dispenser to a solution containing 20 g. of the 6-carboethoxy-2-aminobenzoic acid hydrochloride,[8] during (0.092 mole) a period of some thirty minutes. The reaction proceeded readily as evidenced by the precipitation in a few minutes of a white solid. After cooling the precipitate was filtered and washed with a small amount of cold water; yield 16.5 g. (81%). A portion recrystallized from aqueous alcohol gave a colorless crystalline compound, m. p. 188–190°.

Anal. Calcd. for $C_{10}H_7O_5N$: C, 54.3; H, 3.17; neut. equiv., 110.5. Found: C, 54.1; H, 3.19; neut. equiv., 115.

Methyl 2,4-Dioxo-1-methyl-3,1,4-benzoxazine-5-carboxylate.—A suspension of 4.7 g. (0.0021 mole) of methyl 2,4-dioxo-3,1,4-benzoxazine-5-carboxylate in 10 ml. of dry ether was placed in a three-necked flask equipped with a dropping funnel, a drying tube and a mechanical stirrer. Ten ml. of an ice-cold ethereal solution of diazomethane prepared from 1.0 g. of nitrosomethylurea was introduced into the flask with constant stirring which was continued for a period of three hours; nitrogen gas was evolved in the early stages of the reaction. The precipitate was removed by filtration, washed with a small amount of dry ether; yield 3.2 g. (64%).

Anal. Calcd. for $C_{11}H_9O_5N$: C, 56.2; H, 3.83. Found: C, 55.8; H, 3.90.

1-Methyl-2,4-quinazolinedione-5-carboxylic Acid.—To a suspension of 2.1 g. (0.009 mole) of methyl 2,4-dioxo-1-methyl-3,1,4-benzoxazine-5-carboxylate in 10 ml. of water was slowly added with constant stirring 50 ml. of a 10% potassium hydroxide solution. After standing for a few minutes the mixture was neutralized with 6 *N* hydrochloric acid and then acidified with 1.5 ml. of 6 *N* hydrochloric acid. One gram of potassium cyanate was then stirred into the mixture. After standing, 1.0 g. (45%) of light yellow colored crystals was deposited which were identified as 2-(N^3-methyl)-ureido-6-carbomethoxybenzoic acid. These were used immediately in the next step.

Anal. Calcd. for $C_{11}H_{12}O_5N_2$: neut. equiv., 126. Found: neut. equiv. (by back titration), 128.

The 2-(N^3-methyl)-ureido-6-carbomethoxybenzoic acid (0.8 g., 0.003 mole) together with 1.5 ml. of concd. hydrochloric acid and 1 ml. of water were heated on a water-bath with occasional stirring for ten minutes. The mixture which soon solidified was refluxed with 15 ml. of 6 *N* hydrochloric acid for an hour to complete the hydrolysis of the ester. The insoluble hydrolysis product was removed by filtration and redissolved in alkali and again filtered to remove any insoluble residue. Upon acidification of the filtrate with hydrochloric acid 0.5 g. (71%) of needles were obtained. Recrystallization from alcohol gave a product m. p. 320–321° (uncorrected).

Anal. Calcd. for $C_{10}H_8O_4N_2$: C, 54.5; H, 3.66; neut. equiv., 220. Found: C, 54.5; H, 3.64; neut. equiv., 215.

The 6-Carbomethoxy-(N-methylammoniumcarboxy)-anthranilic-methylamide and 3-Amino-N-methylphthalimide.—Six grams (0.027 mole) of methyl-2,4-dioxo-3,1,4-benzoxazine-5-carboxylate was added slowly with constant stirring to 40 ml. of an ice-cold saturated solution of methylamine in methanol. This gave a clear yellow solution from which yellow crystals began to separate. After thirty minutes the crystals were removed by filtration; yield 1.3 g. These crystals were identified as 3-amino-N-methylphthalimide, m. p. 201°.

Anal. Calcd. for $C_9H_8O_2N_2$: C, 61.3; H, 4.54; N, 15.9. Found: C, 61.4; H, 4.59; N, 15.5.

The filtrate was then evaporated under reduced pressure to a small volume from which the crystalline product separated on cooling. This product was removed by filtration and recrystallized from ethereal alcohol; yield 1.7 g. (22%). The colorless crystalline compound melted at 136° with gas evolution, resolidified and remelted at 198–200°.

Anal. Calcd. for $C_{12}H_{17}O_5N_3$: C, 50.8; H, 6.01. Found: C, 51.0; H, 6.23.

3-Methyl-2,4-quinazolinedione-5-carboxylic Acid.—A solution of 0.7 g. (0.0025 mole) of 6-carbomethoxy-(N-methylammoniumcarboxy)-anthranilic-methylamide in 10 ml. of 6 *N* hydrochloric acid was heated on a water-bath with constant stirring for five minutes. Crystals soon separated which were collected after cooling; yield 0.55 g. (95%). Upon recrystallization from alcohol, the compound gave a m. p. of 190–193° with sublimation and was identified as the ester methyl 3-methyl-2,4-quinazolinedione-5-carboxylate.

Anal. Calcd. for $C_{11}H_{10}O_4N_2$: C, 56.4; H, 4.27. Found: C, 56.0; H, 4.26.

The ester was hydrolyzed by refluxing in concd. hydrochloric acid to 3-methyl-2,4-quinazolinedione-5-carboxylic acid, m. p. 332–333° (uncor.). The compound was judged to be identical with the monomethyl-2,4-quinazolinedione-5-carboxylic acid prepared by partial methylation of 2,4-quinazolinedione-5-carboxylic acid with dimethyl sulfate[2] on basis of a mixed melting point determination.

Methylation of ?-Methyl-2,4-quinazolinedione-5-carboxylic Acid.—Eighty-five mg. (0.000386 mole) of (?-methyl-2,4-quinazolinedione-5-carboxylic acid was added slowly with constant stirring to 10 ml. of an ice-cold ethereal solution of diazomethane prepared from 1.0 g. of N-nitrosomethylurea; nitrogen gas was slowly evolved as the mixture was gradually warmed up to room temperature. After standing for five hours, the evolution of gas ceased and the solution was evaporated then to half its original volume and filtered; yield 60 mg. This neutral product recrystallized from alcohol and gave a m. p. of 193–195°.

Anal. Calcd. for $C_{11}H_{10}O_4N_2$: C, 56.4; H, 4.28. Found: C, 56.6; H, 4.60.

Thirty mg. of the above neutral product was remethylated with 10 ml. of an ice-cold ethereal solution of N-nitrosomethylurea and 5 ml. of dry methanol under same conditions. Upon completion of the reaction the solution was evaporated to dryness and redissolved in hot alcohol–water mixture. After cooling for several days in the refrigerator, 5 mg. of a crystalline compound was obtained; m. p. 136–137°.

Anal. Calcd. for $C_{12}H_{12}O_4N_2$: C, 58.1; H, 4.63. Found: C, 58.3; H, 4.77.

3-Methylamino-N-methylphthalimide.—A 1.0-g. sample of methyl 2,4-dioxo-1-methyl-3,1,4-benzoxazine-5-carboxylate (prepared from diazomethane methylation

(7) All melting points corrected unless otherwise stated.

(8) Bogert, THIS JOURNAL, **31**, 486 (1909).

of methyl 2,4-dioxo-3,1,4-benzoxazine-5-carboxylate) was suspended in 10 ml. of ethyl alcohol cooled by an ice-bath; 15 ml. of a saturated alcoholic solution of methylamine was added gradually with stirring. After the addition, stirring was continued for half an hour, while intensely yellow colored solid began to appear. The product was removed by filtration and additional product was obtained by evaporation of the mother liquor. The combined products were recrystallized from alcohol; yield 0.85 g., m. p. 158°. The product remained unchanged after refluxing with either concentrated hydrochloric acid or potassium hydroxide.

Anal. Calcd. for $C_{10}H_{10}O_2N_2$: N, 14.74. Found: N, 14.70.

Summary

The 1-methyl-2,4-quinazolinedione, m. p. 147°, reported by Abt was shown to be a mixture of product m. p. 265° and starting material. Scott and Cohen's dimethyl-2,4-quinazolinedione-5-carboxylic acid was identified as the 3-methyl-2,4-quinazolinedione-5-carboxylic acid.

Both the 1-methyl-2,4-quinazolinedione-5-carboxylic acid and its 3-methyl isomer were made by methods which established their structures.

CORVALLIS, OREGON RECEIVED APRIL 22, 1950

[CONTRIBUTION FROM THE CHEMOTHERAPY DIVISION, STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

The Preparation of Heterocyclic Sulfonamides[1]

BY RICHARD O. ROBLIN, JR., AND JAMES W. CLAPP

In connection with a study of carbonic anhydrase inhibitors,[2] it occurred to us that heterocyclic sulfonamides might possess a high degree of inhibitory action. This idea was based on the assumption that a competition between carbon dioxide or bicarbonate ion and the sulfonamide group might account for the known inhibitory action of sulfanilamide and other unsubstituted sulfonamides on this enzyme.[3] A direct relationship had been established previously between the acid dissociation constants of sulfanilamide derivatives and their competitive antagonism of *p*-aminobenzoic acid.[4] Consequently, although no evidence for a competitive effect is known in the case of carbonic anhydrase,[5] it was anticipated that heterocyclic sulfonamides would be more highly acidic and might therefore exert a more powerful inhibitory action.

The present report deals with the preparation of heterocyclic sulfonamides unsubstituted on the sulfonamide nitrogen, since unsubstituted derivatives are the only type which have been reported to produce a high degree of enzymic inhibition.[3] The same approach has also been applied to the synthesis of substituted derivatives.

Relatively few heterocyclic sulfonamides in which the sulfur atom is joined directly to a carbon of the heterocyclic ring have been described. They have usually been prepared by chlorosulfonation or conversion of a sulfonic acid to the acid chloride, followed by amidation, methods which are not generally applicable to the synthesis of heterocyclic sulfonamides. On the other hand, the low temperature oxidative chlorination of thio heterocycles, followed by amidation of the sulfonyl chlorides, has been found to be quite widely applicable to the preparation of these compounds. This procedure has been employed previously in the synthesis of aromatic and aliphatic sulfonyl chlorides and 5-acetylaminopyridine-2-sulfonyl chloride.[6]

Some exceptions have been encountered in the general application of the low temperature oxidative chlorination method to the preparation of heterocyclic sulfonyl chlorides. For example, none of the thiouracils or thiotriazines investigated could be converted to the acid chlorides. In the case of 2-thiouracil, only 5-chlorouracil[7] could be identified in the reaction mixture. Similarly, the presence of free amino groups or partially saturated ring systems also appeared to interfere with the normal course of the reaction. The instability of many of the sulfonyl chlorides may account for these exceptions, and for the wide variations in yields obtained in the successful cases. On standing, particularly in an impure state, most of the heterocyclic acid chlorides decompose rapidly with the loss of sulfur dioxide. With the compounds investigated, namely, benzothiazole-2-sulfonyl chloride, 4,6-dimethylpyrimidine-2-sulfonyl chloride and 1-methyltetrazole-5-sulfonyl chloride, the decomposition products were found to be the corresponding chloro derivatives, such as 2-chlorobenzothiazole. This compound has been reported to be the primary product of the chlorination of 2-thiobenzothiazolone when the reaction is carried out for long periods of time at room temperature.[8]

Because of the instability of the sulfonyl chlorides, the crude products were usually converted directly to the more stable sulfonamides by amidation in liquid ammonia. In this manner, a num-

(1) Presented in part before the Division of Medicinal Chemistry at the Philadelphia Meeting of the American Chemical Society, April 10, 1950.

(2) Miller, Dessert and Roblin, THIS JOURNAL, **72**, 4893 (1950).

(3) Mann and Keilin, *Nature*, **146**, 164 (1940); Krebs, *Biochem. J.*, **43**, 525 (1948).

(4) Bell and Roblin, THIS JOURNAL, **64**, 2905 (1942).

(5) *Cf.* Davenport, *J. Biol. Chem.*, **158**, 567 (1945).

(6) Schiller and Otto, *Ber.*, **9**, 1638 (1876); Zincke and Frohneberg, *ibid.*, **42**, 2722 (1909); Douglass and Johnson, THIS JOURNAL, **60**, 1486 (1938); Caldwell and Kornfeld, *ibid.*, **64**, 1695 (1942).

(7) Johnson, *Am. Chem. J.*, **40**, 19 (1908).

(8) Findlay and Dougherty, THIS JOURNAL, **68**, 1666 (1946).