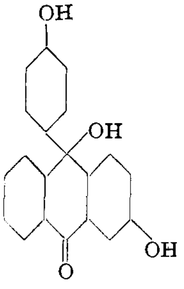
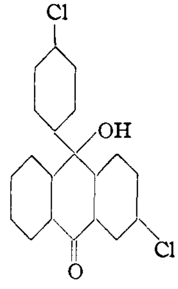
[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

A Further Study of 2-(4″-Hydroxybenzoyl)-4′-hydroxybenzophenone[1]

BY F. F. BLICKE AND R. A. PATELSKI[2]

Baeyer[3] treated the compound which he thought was (I) 3,9-dihydroxy-9-(4′-hydroxyphenyl)-anthrone-10 with phosphorus pentachloride and obtained a substance which he called 3-chloro-9-hydroxy-9-(4′-chlorophenyl)-anthrone-10 (II); upon reduction of the latter substance he stated that 3-chloro-9-(4′-chlorophenyl)-anthrone-10 (III) was produced which, upon further reduction, yielded 3-chloro-9-(4′-chlorophenyl)-10-hydroxy-9,10-dihydroanthracene (IV).[4]


I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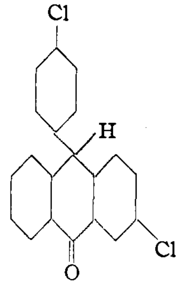
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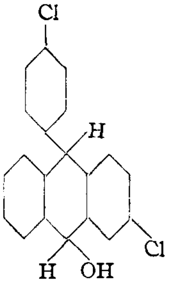
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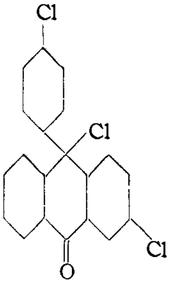
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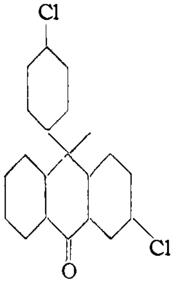
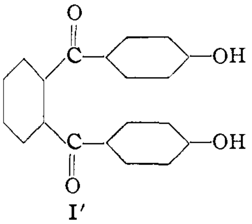
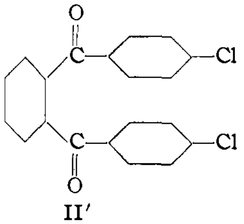

VI

In reality the material which Baeyer treated with phosphorus pentachloride was 2-(4″-hydroxybenzoyl)-4′-hydroxybenzophenone (I′)[5] and this was converted by the phosphorus compound into 2-(4″-chlorobenzoyl)-4′-chlorobenzophenone (II′) from which there is obtained, by reduction, 2,4-di-(*p*-chlorophenyl)-3,4-benzofuran (III′); further reduction yields a substance which is probably 2,5-di-(*p*-chlorophenyl)-2,5-dihydro-3,4-benzofuran (IV′).


I′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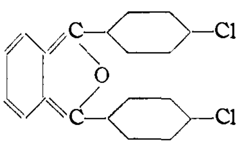
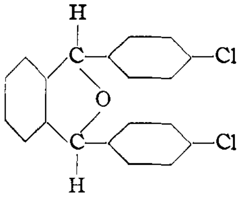

III′


IV′

We have prepared the true 3-chloro-9-hydroxy-9-(4′-chlorophenyl)-anthrone-10 (II) and the 3-chloro-9-(4′-hydroxyphenyl)-anthrone-10 (III) and have shown that their melting points are entirely different from those reported for these compounds. The tertiary carbinol II was converted into its methyl ether and into the carbinol chloride V. The latter, dissolved in benzene, reacted instantly with molecular silver to yield a deep red solution of the free radical (VI) which became decolorized when exposed to air.[6] When a benzene solution of the carbinol chloride was shaken with molecular silver the carbinol chlorine was removed quantitatively in fifteen minutes; when a mixture of the chloride, bromobenzene and silver was shaken vigorously in an absorption apparatus filled with oxygen, reaction with the gas began at once and after fifteen minutes the calculated quantity of oxygen for peroxide formation had been absorbed. The crystalline peroxide of the free radical was analyzed.

When phenolphthalein was treated with phosphorus pentachloride in accordance with Baeyer's directions[7] we did not obtain 4,4′-dichlorodiphenyl phthalide although Baeyer did undoubtedly isolate this compound; instead there was produced 3,9-dichloro-9-(4′-chlorophenyl)-anthrone-10 (V). The anthrone formation is in accord with the experience of Schlenk and Bergmann.[8] These inves-

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(1) This paper represents part of a dissertation to be submitted to the Graduate School by R. A. Patelski in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) The Upjohn Company Fellow.

(3) Baeyer, *Ann.*, **202**, 109 (1880).

(4) According to the peculiar terminology used by Baeyer compound I is Phtalideïn des Phenols; compound II, Phenolphtalideïn Chlorid; compound III, Phenolphthalidinchlorid; and compound IV, Chlorid des Hydrophtalidins.

(5) Blicke and Weinkauff, THIS JOURNAL, **54**, 1454 (1932).

(6) The free radical obtained from 9-chloro-9-phenylanthrone-10 has been studied by Liebermann, Glawe and Lindenbaum [*Ber.*, **37**, 3340 (1904)] and by Schlenk [*Ann.*, **394**, 191 (1912)].

(7) Baeyer, *ibid.*, **202**, 75 (1880).

(8) Schlenk and Bergmann, *ibid.*, **463**, 150 (1928).

tigators allowed diphenylphthalide to react with phosphorus pentachloride and then treated the reaction product with methyl alcohol whereupon 9-methoxy-9-phenylanthrone-10 was obtained.

4′,4″-Dichlorodiphenylphthalide was synthesized from phthalyl chloride, chlorobenzene and aluminum chloride. This compound was reduced to 4′,4″-dichlorodiphenylphthalin and the latter treated with sulfuric acid whereupon 3-chloro-9-(4′-chlorophenyl)-anthrone-10 (III) was formed. This substance was oxidized to the corresponding carbinol (II) and the latter converted into the carbinol chloride with the aid of hydrogen chloride.

Hitherto the proof of the structure of 2-(4″-hydroxybenzoyl)-4′-hydroxybenzophenone has been based on the formation of a diphenylhydrazone, a dioxime, a benzopyridazine and upon the synthesis of the dimethyl ether of the diketone by interaction of 4-anisylmagnesium iodide with phthalic anhydride and with methyl 2-(4′-methoxybenzoyl)-benzoate, respectively.[9] We have now furnished additional proof of the structure of the diketone dimethyl ether (which can be demethylated readily) through its synthesis by two different methods: (a) 2-cyanoethyl benzoate was treated with 4-anisylmagnesium iodide (interaction of 2-cyanoethyl benzoate with phenylmagnesium bromide yielded 2-benzoylbenzophenone); (b) from 4′-methoxyphenylphthalide and 4-anisylmagnesium iodide there was obtained 2,5-di-(*p*-methoxyphenyl)-3,4-benzofuran which, when oxidized, was converted into the diketone dimethyl ether.

Experimental Part

2-(4″-Chlorobenzoyl)-4′-chlorobenzophenenone (II′).—A mixture of 16 g. of 2-(4″-hydroxybenzoyl)-4′-hydroxybenzophenone[10] and 80 g. of phosphorus pentachloride was heated in an oil-bath at 120–125° until no more hydrogen chloride was evolved. Water was added cautiously to the cold mixture, the semi-solid product washed with water and triturated with warm, dilute sodium hydroxide solution. The alkali-insoluble portion was recrystallized from acetic acid; m. p. 167–168°;[11] yield 14 g.

Anal. Calcd. for $C_{20}H_{12}O_2Cl_2$: Cl, 19.99. Found: Cl, 19.91.

The diphenylhydrazone was obtained when a mixture of 2 g. of the ketone, 150 cc. of alcohol and 5 g. of phenylhydrazine was heated on a steam-bath for twelve hours. The yellow, crystalline product was recrystallized from acetone; yield 2.6 g.; m. p. 202–203° with decomposition.

Anal. Calcd. for $C_{32}H_{24}N_4Cl_2$: Cl, 13.26. Found: Cl, 12.98.

2,5-Di-(*p*-chlorophenyl)-3,4-benzofuran (III′).—Seven grams of 2-(4″-chlorobenzoyl)-4′-chlorobenzophenone, 750 cc. of acetic acid and 50 g. of zinc dust were refluxed for two hours. The hot, highly fluorescent solution was filtered and the yellow, crystalline compound which separated from the filtrate dried in a vacuum desiccator. More material can be obtained by dilution of the filtrate with water. After recrystallization from acetic acid the furan melted at 199–200°;[12] yield 4 g.

Anal. Calcd. for $C_{20}H_{12}OCl_2$: Cl, 20.93. Found: Cl, 20.80.

4′,4″-Dichlorodiphenylphthalide.—To a mixture of 40 g. of phthalyl chloride and 225 g. of chlorobenzene there was added 35 g. of aluminum chloride. After six hours the material was poured on ice, steam distilled to remove excess chlorobenzene and the light brown solid residue recrystallized from acetic acid; yield 60 g. The colorless crystals melted at 157–158°.[13]

Baeyer stated that he prepared this phthalide from phenolphthalein and phosphorus pentachloride. However, when we repeated Baeyer's experiment, heated the crude reaction product with 30% sodium hydroxide solution and recrystallized the material from acetic acid there was obtained 3-chloro-9-hydroxy-9-(4′-chlorophenyl)-anthrone-10 (mixed m. p. 223–224°) instead of the dichlorophthalide.

4′,4″-Dichlorodiphenylphthalin.—Forty grams of 4′,4″-dichlorodiphenylphthalide, dissolved in 500 cc. of alcohol, was mixed with 300 cc. of 50% alcoholic sodium hydroxide solution, 300 cc. of water and then 200 g. of zinc dust added. The mixture was refluxed on a steam-bath for twelve hours. At the end of this time sufficient alcohol should be present to keep all of the organic material in solution. The hot mixture was filtered, the alcohol removed from the filtrate and the gummy residue heated with a mixture of 100 cc. of hydrochloric acid and 50 cc. of water. The white, crystalline solid obtained was recrystallized from alcohol; m. p. 205–206°.[14] The product was completely soluble in dilute sodium carbonate solution.

3-Chloro-9-(4′-chlorophenyl)-anthrone-10 (III).—Ten grams of finely powdered 4′,4″-dichlorophenylphthalin was added to 30 cc. of concd. sulfuric acid, the mixture stirred for twenty minutes and the greenish yellow solution poured into 400 cc. of water; the mixture was then boiled for a short time. The amber colored precipitate exhibited a slight greenish yellow fluorescence when dissolved in organic solvents due, no doubt, to the presence of a trace of the furan. After recrystallization from alcohol the colorless crystals melted at 143–144°; yield 8.5 g.

Anal. Calcd. for $C_{20}H_{12}OCl_2$: Cl, 20 93. Found: Cl, 20.64.

3-Chloro-9-hydroxy-9-(4′-chlorophenyl)-anthrone-10 (II).—A solution of 7 g. of sodium dichromate in 15 cc. of water was added to 8.5 g. of the anthrone de-

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[9] Blicke and Weinkauff, THIS JOURNAL, **54**, 1454 (1932).

[10] Blicke and Weinkauff, *ibid.*, **54**, 1457 (1932).

[11] Baeyer [*Ann.*, **202**, 109 (1880)] reported the melting point as 156°.

[12] Baeyer [*ibid.*, **202**, 96 (1880)] stated that the compound melts at about 170°.

[13] Baeyer [*ibid.*, **202**, 76 (1880)] recorded the melting point as 155–156°.

[14] Our procedure is a variation of that described by Baeyer [*Ann.*, **202**, 84 (1880)]; he reported the melting point to be 205–206°.

scribed above, dissolved in 100 cc. of acetic acid. After the rather vigorous reaction had subsided the mixture was heated on a steam-bath for fifteen minutes, 300 cc. of water added, the crystalline precipitate filtered and recrystallized from acetic acid; the colorless product melted at 223–224°; yield 7.0 g. The same melting point was obtained when the product was mixed with the material formed by interaction of phosphorus pentachloride and phenolphthalein.

Anal. Calcd. for $C_{20}H_{12}O_2Cl_2$: Cl, 19.99. Found: Cl, 20.14.

The hydroxyanthrone dissolves in concd. sulfuric acid to form a deep permanganate colored solution.

3,9-Dichloro-9-(4′-chlorophenyl)-anthrone-10 (V).—To 25 g. of the carbinol (II), suspended in 200 cc. of dry benzene, there was added 20 cc. of acetyl chloride; the mixture was heated to the boiling point and treated with hydrogen chloride for two hours. The solvent was removed from the solution under reduced pressure and 10 cc. of petroleum ether (30–60°) added to the sirupy residue. After crystallization the product was recrystallized from petroleum ether (90–100°); yield 18.5 g.; m. p. 121–122°.

Anal. Calcd. for $C_{20}H_{11}OCl_3$: Cl, 28.49. Found: Cl, 28.68.

In order to obtain the carbinol ether 1 g. of the carbinol chloride was dissolved in 10 cc. of absolute methyl alcohol and boiled for a few minutes. The ether separated in crystalline form and was recrystallized from acetic acid; m. p. 165–166°; yield 0.9 g.

Anal. Calcd. for $C_{21}H_{14}O_2Cl_2$: Cl, 19.22. Found: Cl, 19.01.

The ether was also obtained when the carbinol, suspended in methyl alcohol, was treated with hydrogen chloride.

The Free Radical, 3-Chloro-9-(4′-chlorophenyl)-anthronyl-10 (VI).—It was found that the carbinol chlorine was removed completely when 1.16 g. of the chloride, dissolved in 55 cc. of dry benzene, was shaken slowly for fifteen minutes with 3 g. of molecular silver (40–60 mesh): calcd. AgCl, 0.45 g.; found AgCl, 0.46 g.

The peroxide of the radical was obtained when 4.5 g. of the chloride, 30 cc. of benzene and 12 g. of silver were shaken for fifteen minutes, the deep red solution filtered and, after the color had changed to a light yellow, the filtrate was treated with petroleum ether (30–60°). After recrystallization from a mixture of equal parts of alcohol and ethyl acetate the peroxide melted at 255–265° with decomposition.

Anal. Calcd. for $C_{40}H_{22}O_4Cl_4$: Cl, 20.04. Found: Cl, 19.39.

A mixture of 1.125 g. of the chloride, 20 cc. of bromobenzene and 3 g. of silver was shaken vigorously in an absorption apparatus filled with oxygen. After fifteen minutes 33.9 cc. (N. T. P.) of oxygen had been absorbed; calcd. for peroxide formation, 33.8 cc.

2-Cyanoethyl Benzoate.—A solution of 16.3 g. of ethyl anthranilate in 35 cc. of hydrochloric acid and 150 cc. of water was diazotized with 6.9 g. of sodium nitrite, dissolved in 20 cc. of water. Cuprous cyanide was prepared from 25 g. of copper sulfate according to "Organic Syntheses."[15] The diazonium solution was neutralized to congo red with sodium carbonate and added to the cuprous cyanide, the mixture stirred vigorously and the temperature maintained at 20–30°. After one-half hour the temperature was raised to 60–70°, the mixture stirred for one hour, cooled, the solid precipitate separated, washed with water, dissolved in benzene, filtered and the solvent removed from the filtrate. The cyanide boiled at 282–286° under 743 mm. pressure. The distillate was washed with low boiling petroleum ether and recrystallized from petroleum ether (90–100°); m. p. 68–69°;[16] yield 8.5 g.

Ethyl anthranilate exhibits local anesthetic action when placed on the tip of the tongue but this action is not possessed by 2-cyanoethyl benzoate; the latter compound tastes similar to celery seeds.

Reaction of 2-Cyanoethyl Benzoate with (a) Phenylmagnesium Bromide and with (b) 4-Anisylmagnesium Iodide.—(a) To phenylmagnesium bromide, prepared from 18.9 g. of bromobenzene, 2.9 g. of magnesium and 70 cc. of ether, there was added 5.2 g. of 2-cyanoethyl benzoate dissolved in 30 cc. of ether. The mixture was heated for one and one-half hours on a steam-bath, the crystalline precipitate filtered, decomposed with ice and ammonium chloride and the crystalline ketone imine recrystallized from methyl alcohol; m. p. 193–194°; yield 7 g.

One gram of the imine, 5 cc. of alcohol, 5 cc. of water and 3 cc. of hydrochloric acid were refluxed for one hour, water added, the precipitate dissolved in methyl alcohol, the solution boiled with charcoal and filtered. The colorless, crystalline precipitate of 2-benzoylbenzophenone obtained melted at 146–147°.[17] To obtain the diphenylhydrazone 0.5 g. of the diketone, 0.8 g. of phenylhydrazine, 20 cc. of alcohol and three drops of acetic acid were refluxed for one hour; the colorless, crystalline product, recrystallized from benzene, melted at 174–176°[18] with decomposition.

(b) To the cooled Grignard reagent obtained from 25.7 g. of 4-iodoanisole, 100 cc. of ether, 25 cc. of benzene and 2.6 g. of maguesium there was added 8.7 g. of 2-cyanoethyl benzoate, dissolved in 60 cc. of ether. The mixture was heated for three hours, the crystalline precipitate filtered and decomposed. The crystalline imine, after recrystallization from alcohol, melted at 169–170° with decomposition; yield 11.5 g.

Ten grams of the imine was heated for ten minutes with 30 cc. of acetic acid and 10 cc. of hydrochloric acid, water added and the semi-solid precipitate warmed with a small amount of alcohol, whereupon it became crystalline; after recrystallization from alcohol the 2-(4″-methoxybenzoyl)-4′-methoxybenzophenone melted at 157–159°.

2,5-Di-(*p*-methoxyphenyl)-3,4-benzofuran from 4′-Methoxyphenylphthalide and 4-Anisylmagnesium Iodide.—4-Anisylmagnesium iodide was prepared from 23.4 g. of carefully fractionated 4-iodoanisole, 2.4 g. of magnesium and 90 cc. of ether; 22.8 g. of the phthalide, dissolved in 100 cc. of benzene, was added. After three hours ammonium chloride solution was added. The colorless ether layer rapidly turned yellow and possessed a greenish

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(15) "Organic Syntheses," Vol. IV, 1925, p. 69.

(16) Müller [*Ber.*, **19**, 1498 (1886)] reported 70°.

(17) Guyot and Catel [*Bull. soc. chim.*, [3] **35**, 1138 (1906)] reported 146°.

(18) Guyot and Catel [ref. 17] reported the melting point to be 165°.

fluorescence. The ether layer was separated, the ether removed and the yellow, oily residue treated with methyl alcohol, whereupon it became crystalline. After recrystallization from a mixture of methyl alcohol and acetone the furan melted at 125–126°;[19] yield 22 g. The oxidation of the furan has been described previously.

Summary

Compounds described erroneously in the literature as (a) 3,9-dihydroxy-9-(4′-hydroxyphenyl)-anthrone-10, (b) 3-chloro-9-hydroxy-9-(4′-chlorophenyl)-anthrone-10, (c) 3-chloro-9-(4′-chlorophenyl)-anthrone-10 and (d) 3-chloro-9-(4′-chlorophenyl) - 10 - hydroxy - 9,10 - dihydroanthracene are, in reality, (a) 2-(4″-hydroxybenzoyl)-4′-hydroxybenzophenone, (b) 2-(4″-chlorobenzoyl)-4′-chlorobenzophenone, (c) 2, 4 - di - (*p*-chlorophenyl)-3,4-benzofuran and (d) 2, 5 - di - (*p*-chlorophenyl)-2,5-dihydro-3,4-benzofuran, respectively.

A few derivatives of 3,9-dichloro-9-(4′-chlorophenyl)-anthrone-10, including the free radical 3-chloro - 9 - (4′ - chlorophenyl) - anthronyl - 10, have been studied.

Two additional syntheses of 2-(4″-hydroxybenzoyl)-4′-hydroxybenzophenone, in the form of its dimethyl ether, have been described.

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[19] Mixed with a sample (m. p. 126–127°) prepared by another method [Blicke and Weinkauff, THIS JOURNAL, **54**, 1458 (1932)] the melting point was found to be that recorded above.

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

The Action of Sulfuric Acid on Diarylphthalins. I[1]

BY F. F. BLICKE AND R. A. PATELSKI[2]

It was stated by Baeyer[3] that treatment of tetrabromophenolphthalin with sulfuric acid yields 2,4 - dibromo - 3 - hydroxy - 9 - (3′,5′ - dibromo - 4′-hydroxyphenyl)-anthrone-10 ("tetrabromophenolphtalidin") and that this compound, when oxidized, is converted into 2,4-dibromo-3,9-dihydroxy - 9 - (3′,5′ - dibromo - 4′ - hydroxyphenyl)-anthrone - 10 ("tetrabromophenolphtalideïn"). The reaction product actually obtained by the use of sulfuric acid is 2,5-di-(*m*,*m*′-dibromo-*p*-hydroxyphenyl)-3,4-benzofuran and this, upon oxidation, yields 2-(3″,5″-dibromo-4″-hydroxybenzoyl) - 3′,5′ - dibromo - 4′ - hydroxybenzophenone. The deep yellow color of the furan, its intense yellow-green fluorescence when dissolved and its conversion, by oxidation, into a 2-benzoylbenzophenone, furnish proof of its structure.

The constitution of 2-(4″-hydroxybenzoyl)-2′-hydroxybenzophenone has been established definitely.[4] Upon bromination of this substance the resulting tetrabromo substitution product which could hardly be any other than the 3′,3″,5′,5″-tetrabromo derivative, was found to be identical with the material obtained by oxidation of the tetrabromofuran mentioned above.

When the dimethyl ether of isophenolphthalin (2′,4″-dimethoxytriphenylmethane - 2 - carboxylic acid) reacts with sulfuric acid a compound, undoubtedly 2-(2′-methoxyphenyl)-5-(4″-methoxyphenyl)-3,4-benzofuran, forms but not in crystalline state. Upon oxidation the material yields 2-(2″-methoxybenzoyl)-4′-methoxybenzophenone.

In order to prove the structure of this ketone it was synthesized by interaction of 4′-methoxyphenylphthalide with 2-anisylmagnesium iodide and oxidation of the furan, formed as an intermediate product.

It has been stated[5] that tetrabromophenolphthalin can be prepared by reduction of tetrabromophenolphthalein with zinc and sodium hydroxide solution; we found, however, that under these conditions the bromine is removed practically quantitatively[6] and phenolphthalin is produced.

Potassium ferricyanide is a satisfactory agent for the oxidation of alkali-soluble 2,5-diaryl-3,4-benzofurans to 2-benzoylbenzophenones.

Experimental Part

Tetrabromophenolphthalin.—To 20 g. of phenolphthalin, dissolved in 100 cc. of boiling acetic acid, there was added 40 g. of bromine, dissolved in 20 cc. of the same solvent. The mixture was heated for ten minutes, cooled and the precipitate filtered. More material was obtained upon

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[1] This paper represents part of a dissertation to be submitted to the Graduate School by R. A. Patelski in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

[2] The Upjohn Company Fellow.

[3] Baeyer, *Ann.*, **202**, 93 (1880).

[4] Blicke and Weinkauff, THIS JOURNAL, **54**, 1454 (1932); Blicke and Patelski, *ibid.*, **58**, 273 (1936).

[5] Baeyer, *Ann.*, **202**, 85 (1880).

[6] Zinc dust and alkali also remove nuclear bromine from 2′-hydroxy-5′-bromodiphenylphthalide [Blicke and Swisher, THIS JOURNAL, **56**, 924 (1934)]; see also Jacobson and Adams, *ibid.*, **46**, 2790 (1924); *ibid.*, **47**, 2011, 2012 (1925).