

as a solvent, the reaction product forms a char-cake with zinc in the bottom of the flask. With benzene as a solvent, even on prolonged heating, the reaction products continue to dissolve in the solvent.

There is evidence then of reactions subsequent to the formation of β -hydroxy esters and runs of brief periods and minimum reaction temperatures are the most satisfactory. So that, in general, the most satisfactory yields are obtained when the reaction time is limited to the period of most vigorous reaction and when an optimum reaction temperature is secured. Benzene is the best solvent, since it brings the temperature into the necessary range; it also keeps free metal surface available since the reaction products are soluble in it; it obviates the formation of char-cake.

Summary

1. A β -hydroxy synthesis is obtained from α -chloro esters and aldehydes or ketones and zinc, through the action of copper metal or cupric oxide.

2. The catalytic action of copper is accounted for by the formation of an intermediate between copper and the aldehyde or ketone present, which then reacts with the zinc-chloro ester compound of the chloro esters and accelerates the synthesis.

3. Benzene is the best solvent, since it brings the temperature into the necessary range. It also keeps free metal surface available since the products are soluble in it.

Limited reaction time increases yields.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF STANFORD UNIVERSITY]

CYCLIC AMMONO KETONES¹ AND ACID CHLORIDES OF THE QUINOXALINE SERIES

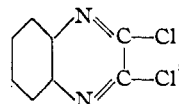
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In a previous communication^{1a} quinoxaline was shown to be formally an ammono glyoxal, and experimental evidence was presented in confirmation of this view. In the present article it is desired to consider a number of derivatives of quinoxaline from the standpoint of the ammonia system, and to give the results of the experimental work supporting the analogies advanced.

2,3-Dichloroquinoxaline.—From its structural formula,

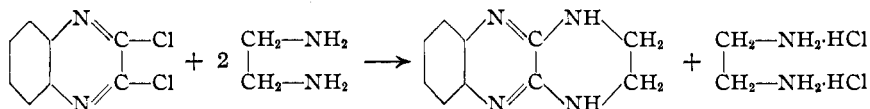


¹ The strict ammonia analogues of the aquo ketones are unknown. Because of the third valence of the nitrogen, all ammono ketones are acetals at the same time. Strain, *THIS JOURNAL*, 49, 1559 (1927).

^{1a} Ogg and Bergstrom, *ibid.*, 53, 245 (1931).

this compound is seen to be a substituted ammono oxalyl chloride,² and hence should show properties analogous to those of acid chlorides. The method of preparation is in accord with this view. 2,3-Dichloroquinoxaline is prepared³ by the action of phosphorus pentachloride on 2,3-dihydroxyquinoxaline, which was shown in the previous communication to be an ester of a mixed aquoammono oxalic acid. This reaction is analogous to the formation of oxalyl chloride from oxalic acid and phosphorus pentachloride.

As an acid chloride, 2,3-dichloroquinoxaline should react with primary and secondary amines, *i. e.*, ammono alcohols, eliminating hydrogen chloride and producing ammono esters. This is actually the case, Hinsberg and Schwantes⁴ having carried out such reactions with various aromatic diamines and with ethylamine. In the present work, a similar reaction has been obtained with ethylenediamine, resulting in a new cyclic ammono ester, *o*-phenylene ethylene oxamidine. It should be mentioned that the



reactivity of 2,3-dichloroquinoxaline is much less than that of aquo acid chlorides.

2,3-Dichloroquinoxaline.—2,3-Dihydroxyquinoxaline was prepared by the method of Meyer and Seelinger,⁵ and converted into 2,3-dichloroquinoxaline by heating with two equivalents of phosphorus pentachloride at 180°, according to the procedure of Hinsberg and Pollak.³

***o*-Phenylene Ethylene Oxamidine.**—Two grams of 2,3-dichloroquinoxaline and 2 g. (three equivalents) of ethylenediamine were sealed in a tube and heated for two hours at 150°. The tube was then opened and the contents were washed with water. The residue was treated with dilute hydrochloric acid, and the solution, after filtration, was rendered alkaline with ammonia. The white precipitate was recrystallized from alcohol in the form of colorless leaves, sparingly soluble in alcohol, insoluble in water, but soluble in acids. Alcoholic solutions showed a faint fluorescence. The melting point was above 350°. The compound was halogen free.

Anal. Subs., 0.0977: 0.09537 *N* HCl (Kjeldahl), 21.90 cc. Calcd. for C₁₀H₁₀N₄: N, 30.09. Found: N, 29.94.

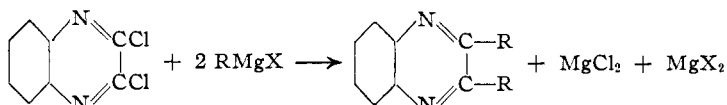
The reaction of an acyl chloride with a Grignard reagent gives as the first product a ketone and magnesium halide. 2,3-Dichloroquinoxaline, as an ammono di-acid chloride (-ester), has been found to react with two equivalents of alkyl magnesium halide, yielding the corresponding ammono diketone (-diacetal), *i. e.*, 2,3-dialkylquinoxaline.

² It is an *o*-phenylene ester and acid chloride of ammono oxalic acid, $\begin{array}{c} \text{NH}=\text{C}-\text{NH}_2 \\ | \\ \text{NH}=\text{C}-\text{NH}_2 \end{array}$

³ Hinsberg and Pollak, *Ber.*, **29**, 784 (1896).

⁴ Hinsberg and Schwantes, *ibid.*, **36**, 4048 (1903).

⁵ Meyer and Seelinger, *ibid.*, **29**, 2641 (1896).



This reaction constitutes a new method of synthesis of such compounds, and was used to prepare 2,3-dimethylquinoxaline and the hitherto unknown 2,3-di-*n*-propylquinoxaline. The latter substance was found to be identical with that prepared by another method (*vide infra*).

The reaction of a considerable excess over two equivalents of methylmagnesium iodide with 2,3-dichloroquinoxaline yielded only a small quantity of 2,3-dimethylquinoxaline and a considerable amount of a red tarry substance, possibly a reduction product of the 2,3-dimethylquinoxaline. It was hoped that 2,2,3,3-tetramethyl-1,2,3,4-tetrahydroquinoxaline might be formed in this reaction.

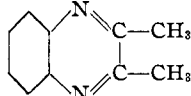
One remarkable fact noted was that 2,3-dichloroquinoxaline did not react at all with phenylmagnesium bromide, even on prolonged refluxing of the ether solution.

2,3-Dimethylquinoxaline.—Three grams of solid 2,3-dichloroquinoxaline was added to an ethereal solution of methylmagnesium iodide (2.1 equivalents). A very vigorous reaction ensued, the 2,3-dichloroquinoxaline dissolving to give a brilliant red solution. After an hour of refluxing, the mixture was decomposed by addition of liquid ammonia, which was then evaporated. The residue was extracted with ether. The red ether solution was steam distilled, the ether first coming over, then a small quantity of unidentified solid, and finally the main product, an oil which readily solidified as fine white needles. This was purified by repeated steam distillation. The substance possessed the peppermint-like odor and the same melting point (106° corr.) as pure 2,3-dimethylquinoxaline, prepared by the method of Gabriel and Sonn.⁶ A mixture of equal quantities of the two melted sharply at 106° (corr.), proving their identity; yield of 2,3-dimethylquinoxaline, 60%.

2,3-Di-*n*-propylquinoxaline.—Five grams of 2,3-dichloroquinoxaline was added to an ethereal solution of *n*-propylmagnesium iodide (2.1 equivalents). A vigorous reaction took place, the solution turning deep brown in color. After two hours, the mixture was treated with ammonia as above, and then extracted with ether. Evaporation of the ether left a dark, mushy residue which was extracted with dilute hydrochloric acid. The acid solution was decolorized with charcoal and then made alkaline with ammonia, whereupon an oil separated. The solution was heated to boiling and filtered with suction, the oil passing through the paper and leaving a slight solid residue. After cooling, the solidified oil was filtered off and pressed on a porous plate. It was dissolved in acetone and reprecipitated by careful addition of water, appearing as white cubical crystals, melting at 42.9° (corr.); yield of 2,3-di-*n*-propylquinoxaline, 30% of the theoretical.

Anal. Subs., 0.0547: 0.09537 *N* HCl (Kjeldahl), 5.40 cc. Calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_2$: *N*, 13.08. Found: *N*, 13.19.

2,3-Dimethylquinoxaline.—It is readily seen from the structure of this

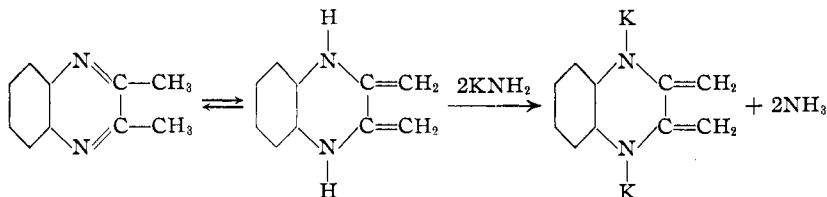
compound, , that it contains two ammono carbonyl groups,

⁶ Gabriel and Sonn, *Ber.*, **40**, 4850 (1907).

$>C=N-$, and is to be regarded as a substituted ammono 1,2-diketone, a substituted ammono diacetyl.⁷ The methods of synthesis are in agreement with the analogy. 2,3-Dimethylquinoxaline was prepared by Gabriel and Sonn⁶ by the action of *o*-phenylenediamine on diacetyl, a reaction which is to be interpreted as the ammonolysis of diacetyl by a substituted ammonia. In this investigation, 2,3-dimethylquinoxaline was synthesized by the action of methylmagnesium iodide on 2,3-dichloroquinoxaline, just as, hypothetically, oxalyl chloride and methylmagnesium iodide should yield diacetyl.⁸ Furthermore, 2,3-dimethylquinoxaline behaves as an ammono diketone on reduction, yielding the corresponding ammono di secondary alcohol, *i. e.*, 1, 2,3,4-tetrahydro-2,3-dimethylquinoxaline.⁹ In addition, 2,3-dimethylquinoxaline yields with benzaldehyde a dibenzal derivative, a type of reaction characteristic of ketones¹⁰ that contain an acetyl group.

Since diacetyl readily adds Grignard reagents^{11a} and hydrocyanic acid,^{11b} similar reactions were attempted with 2,3-dimethylquinoxaline, but without result. Hydrogen cyanide had no effect, while ethereal methylmagnesium iodide caused slow conversion to a red tar not further investigated.

A typical property of ketones having a hydrogen atom on the α -carbon atom is the formation of salts of the enol form through the agency of alkali metals, alcoholates or alkali metal amides. Furthermore, such salts react with alkyl halides, yielding usually metal halide and an α -alkyl derivative of the ketone.¹² In the present investigation, it has been found that the ammono diketone, 2,3-dimethylquinoxaline, behaves in an analogous fashion. Thus it has been found to react with potassium amide in liquid ammonia, giving a well-crystallized dipotassium salt of the ammono dienol modification.



⁷ Mills and Smith, *J. Chem. Soc.*, 121, 2724 (1922), have suggested the strong resemblance between the $\text{CH}_3-\text{C}=\text{N}-$ group of heterocyclic bases and the carbonyl group of the aquo ketones containing a methyl group.

⁶ Actually, oxalyl chloride decomposes so readily into phosgene and carbon monoxide that it does not give this reaction.

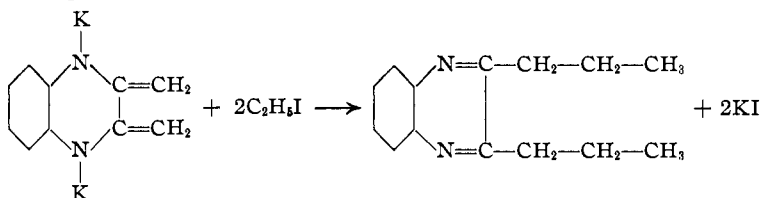
⁹ Gibson, *J. Chem. Soc.*, 342 (1927).

¹⁰ Bennet and Willis, *ibid.*, 1960 (1928).

¹¹ (a) Zelinsky, *Ber.*, 35, 2138 (1902); (b) Fittig, Daimler and Keller, *Ann.*, 249, 208 (1888).

¹² Haller, *Bull. soc. chim.*, 31, 1073 (1922), and other articles.

This salt on hydrolysis yielded unchanged 2,3-dimethylquinoxaline and potassium hydroxide. Furthermore, the salt reacted readily with two equivalents of ethyl iodide, producing potassium iodide and 2,3-di-*n*-propylquinoxaline, found to be identical with that described earlier in this paper. This reaction is seen to be analogous to that undergone by the salts of aquo ketones.¹³



It should be noted that the structure of this new compound has been definitely proved from its synthesis by two entirely different methods.

The above reaction should proceed equally well with other alkyl halides and constitutes a new method for the synthesis of 2,3-dialkylquinoxalines. It is also apparently the first synthesis of this type to be carried out with an ammono diketone.

2,3-Dimethylquinoxaline.—This was prepared by the method of Gabriel and Sonn^{6,14} from *o*-phenylenediamine and diacetyl monoxime, and was purified by steam distillation. The white crystals of the hydrate readily effloresced, and when anhydrous melted at 106° (corr.).

Dipotassium Salt of 2,3-Dimethylquinoxaline.—This was prepared in an ammonia tube, using the technique described by Franklin.¹⁵ One gram of anhydrous 2,3-dimethylquinoxaline was treated with two equivalents of potassium amide in liquid ammonia. The 2,3-dimethylquinoxaline (which was only slightly soluble in pure ammonia) dissolved rapidly to give a clear deep red solution. On cooling in a bath of liquid ammonia, an abundant precipitate of long greenish-yellow crystals formed. These were washed by decantation and recrystallized four times. The final washings were of the same red color as the initial, showing this to be the color of the dissolved salt. The leg containing the salt was evacuated for analysis at 60°. The sample was dissolved in dilute hydrochloric acid and one quarter of the solution was used for each analysis; weight of salt, 1.0280 g.

Anal. Subs., 0.2570: 0.09537 *N* HCl (Kjeldahl), 23.30 cc. Subs., 0.2570: K₂SO₄, 0.1914. Calcd. for C₁₀H₈N₂K₂: N, 11.95; K, 33.37. Found: N, 12.12; K, 33.42.

Qualitative investigation of the products of hydrolysis showed them to be potassium hydroxide and 2,3-dimethylquinoxaline.

2,3-Di-*n*-propylquinoxaline.—One gram of 2,3-dimethylquinoxaline was converted

¹³ The alkylation of quinaldine, which is to be regarded as a substituted ammono ketone, has likewise been carried out by the action of alkyl halides on alkali salts of the ammono-enol modification of quinaldine. Bergstrom, *Science*, **72**, 402 (1930); Ziegler and Zeiser, *Ann.*, **485**, 178 (1931). As to a possible mechanism of alkylations of this type, see Decker, *Helv. Chim. Acta*, **13**, 666 (1930).

¹⁴ Henderson, *J. Chem. Soc.*, 466 (1929).

¹⁵ Franklin, *THIS JOURNAL*, **27**, 831 (1905); **29**, 1694 (1907); **35**, 1460 (1913); *J. Phys. Chem.*, **15**, 510 (1911); **16**, 694 (1912).

into the dipotassium salt by treatment (in an ammonia tube) with two equivalents of potassium amide in liquid ammonia. After evaporation of the ammonia, the tube was evacuated at 50°. A slight excess over two equivalents of ethyl iodide (2 g.) in 10 cc. of absolute ether was sucked into the evacuated tube. A very vigorous reaction ensued, the greenish-yellow crystals being replaced by a fine white precipitate of potassium iodide. The tube was finally warmed for a few minutes at 100°, and then cooled and opened. The contents were washed out with water. The ether layer was separated and evaporated, leaving a brown partially crystalline mass. By suction on a filter some dark oil was removed, leaving cubical crystals. These were pressed on a porous plate, and then dissolved in dilute hydrochloric acid. The solution was decolorized with charcoal and neutralized with ammonia. The precipitate was filtered off (after cooling), again pressed on a plate, and finally precipitated from acetone solution by addition of water. So obtained, the product consisted of colorless cubical crystals, m. p. 42.9° (corr.), very soluble in organic solvents, insoluble in water, soluble in dilute acids. It was slightly volatile with steam.

Anal. Subs., 0.1449, 0.1508; CO₂, 0.4166, 0.4329; H₂O, 0.1125, 0.1149. Subs., 0.1023, 0.1020; 0.09537 *N* HCl, 9.99 cc., 9.92 cc. (Kjeldahl). Calcd. for C₁₄H₁₈N₂: C, 78.47; H, 8.46; N, 13.07. Found: C, 78.39, 78.30; H, 8.69, 8.53; N, 13.05, 12.99.

The above substance was identical in all respects with the 2,3-di-*n*-propylquinoxaline prepared (*vide supra*) from 2,3-dichloroquinoxaline and *n*-propylmagnesium iodide. A mixture of the two gave exactly the same melting point as either constituent: yield by the above reaction, 70% of the theoretical.

The small amount of oily by-product mentioned above decolorized a carbon tetrachloride solution of bromine (a reaction not given by 2,3-di-*n*-propylquinoxaline). It is suggested that this substance may have been the di-*N*-ethyl derivative of the ammono dienol of 2,3-dimethylquinoxaline.

2,3-Diphenylquinoxaline.—In accord with previous analogies, 2,3-diphenylquinoxaline is to be regarded as a substituted ammono aromatic diketone, a substituted ammono benzil. In agreement with this view, it is synthesized¹⁶ by the action of *o*-phenylenediamine on benzil, an ammonolysis of the type before described. Just as benzil on partial reduction yields benzoin, which can be reoxidized to benzil, so 2,3-diphenylquinoxaline gives on gentle reduction 1,2-dihydro-2,3-diphenylquinoxaline,¹⁶ an ammono benzoin, which may also be prepared from benzoin and *o*-phenylenediamine.¹⁷ Upon oxidation, the compound yields 2,3-diphenylquinoxaline.

On strong reduction benzil gives the optically isomeric di-secondary alcohols hydrobenzoin and isohydrobenzoin, while 2,3-diphenylquinoxaline yields the corresponding ammono di-secondary alcohols, racemic and internally compensated 1,2,3,4-tetrahydro-2,3-diphenylquinoxalines.¹⁸

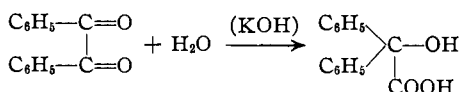
Since benzil adds hydrocyanic acid and Grignard reagents, similar reactions were attempted with 2,3-diphenylquinoxaline, but as in the case of 2,3-dimethylquinoxaline, unsuccessfully.

The most remarkable of the reactions of benzil is the well-known rearrangement in the presence of a base to a salt of benzilic acid.

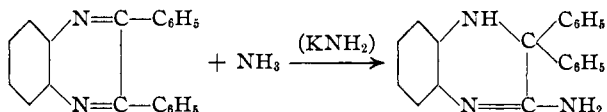
¹⁶ Hinsberg and König, *Ber.*, **27**, 2181 (1894).

¹⁷ O. Fischer, *ibid.*, **24**, 719 (1891).

¹⁸ Bennett and Gibson, *J. Chem. Soc.*, **123**, 1570 (1923).



It has been found that 2,3-diphenylquinoxaline probably undergoes an analogous rearrangement in the presence of the ammonio base potassium amide in liquid ammonia, producing what appears to be the hitherto unknown 1,2-dihydro-2,2-diphenyl-3-aminoquinoxaline, which is to be regarded as a substituted ammono benzoic acid.



Although we were unable to prove this structure by direct synthesis, it is the most probable. If this is the structure, the reaction is the first example of the benzoic acid rearrangement in the ammonia system.

2,3-Diphenylquinoxaline.—This was prepared by the method of Hinsberg and König¹⁶ from benzil and *o*-phenylenediamine.

1,2-Dihydro-2,2-diphenyl-3-aminoquinoxaline.—When 2,3-diphenylquinoxaline, which was practically insoluble in liquid ammonia, was treated with two equivalents of potassium amide in that solvent it dissolved, giving a deep violet solution, but underwent no further change, or at best only a very slow one. (It is worth noting that benzil dissolves in *cold* alcoholic potassium hydroxide to give a deep violet solution.) Heating was therefore employed to accelerate the reaction: 1.2 g. of potassium was converted catalytically into amide in a straight tube containing liquid ammonia; 2.2 g. of diphenylquinoxaline was then added and the tube sealed off, enclosing about 20 cc. of liquid ammonia. The sealed tube was heated in the steel bomb described by Blair¹⁹ for ten hours at 130–140°. The solution was then still colored but contained a precipitate. After evaporation of the ammonia, the residue was treated with water, and the resulting brown solid was washed and dried. It was extracted twice with hot benzene (to remove 2,3-diphenylquinoxaline). The residue was dissolved in alcohol and decolorized with charcoal. By concentrating and cooling the solution, the product was obtained as colorless rhombohedra, fairly soluble in alcohol, insoluble in water and benzene. The substance melted without decomposition at 287° (corr.) and could be sublimed in beautiful colorless flakes. It was basic, giving a crystalline hydrochloride with alcoholic or aqueous hydrochloric acid. It dissolved in concentrated sulfuric acid without color.

Anal. Subs., 0.1417, 0.1491: CO₂, 0.4178, 0.4389; H₂O, 0.0686, 0.0733. Subs., 0.0706, 0.1032: 0.09537 *N* HCl (Kjeldahl), 7.48, 10.90 cc. Calcd. for C₂₀H₁₇N₃: C, 80.24; H, 5.72; N, 14.04. Found: C, 80.41, 80.28; H, 5.42, 5.50; N, 14.16, 14.11.

Thus the substance is seen to have the correct composition for the expected 1,2-dihydro-2,2-diphenyl-3-aminoquinoxaline. This is the most probable structure for the new compound, in view of its stability and high melting point. Oddly enough, the substance did not react with nitrous acid. Also, it was unaffected by heating with alcoholic hydrochloric acid at 150°. It is realized that in view of these facts some doubt may be cast upon the structure assigned, and attempts will be made to prove this structure by direct syntheses. The yield was 30% but much of the diphenylquinoxaline was recovered unchanged.

¹⁹ Blair, *THIS JOURNAL*, **48**, 87 (1926).

Summary

2,3-Dichloroquinoxaline, 2,3-dimethylquinoxaline and 2,3-diphenylquinoxaline have been shown to be substitution products, respectively, of an ammono oxalyl chloride, an ammono diacetyl and an ammono benzil, and experimental evidence confirming this view has been presented.

Two new methods for the synthesis of 2,3-dialkylquinoxalines have been developed.

The alkylation of an ammono diketone by converting it into a salt of the ammono dienol modification and treating this with an alkyl halide has been carried out for the first time.

Evidence of a benzylic acid rearrangement of an ammono benzil has been found.

The following new compounds have been prepared: *o*-phenylene ethylene oxamidine, 2,3-di-*n*-propylquinoxaline, the dipotassium salt of 2,3-dimethylquinoxaline dienol, 1,2-dihydro-2,2-diphenyl-3-aminoquinoxaline (structure not definitely proven).

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[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

SOME RELATIONSHIPS OF THE RATIO OF REACTANTS TO THE EXTENT OF CONVERSION OF BENZALDEHYDE AND FURFURALDEHYDE TO THEIR ACETALS

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Most of the measurements which have been made in this Laboratory upon the relationship of the structure of aldehydes and alcohols to the extent of the acetal reaction have been made upon mixtures resulting from the reaction of approximately eleven moles of alcohol with one mole of aldehyde.¹ This ratio of reactants was originally selected in order to preserve the homogeneity of the reaction mixtures, and has been used in other cases in order to obtain a direct comparison of the extent of conversion of various pairs of reactants. More recently it has seemed desirable to ascertain to what extent, if at all, the calculated equilibrium constants for this reaction are dependent upon the ratio of reactants. Such a study has now been made for certain of the acetals of benzaldehyde and furfuraldehyde.

The Reaction of Benzaldehyde with Alcohols.—Test-tubes (1 × 15 cm.) so marked as to make it easy to measure into them approximately the desired volume of alcohol and benzaldehyde, were drawn out preparatory to

¹ Adkins, Adams, Hartung, Street and Broderick, *THIS JOURNAL*, **47**, 1358 (1925); **49**, 2517 (1927); **50**, 162 (1928); **50**, 178 (1928).