Absence of the powerful meta-directing influence of the sodium ion in the furan nucleus suggests that it is overcome by a strong ortho-directing influence such as an ether linkage inside the ring.

Polarographically Controlled Syntheses, with Particular Reference to Organic Chemistry

BY JAMES J. LINGANE, C. GARDNER SWAIN AND MELVIN FIELDS[1]

Electrolytic preparative methods, particularly in the field of organic chemistry, have not been exploited to the extent that their inherent advantages would seem to warrant. This is chiefly attributable to the difficulties of predicting, by the classical procedures, optimum conditions of electrolysis, and the consequent necessity of performing an inordinately large number of laborious trial-and-error experiments to establish even approximately correct conditions. The highly empirical character of the organic electrochemical preparative literature is well reflected in the almost universal custom of specifying current density as a variable of purportedly great importance, although actually it has only minor significance unless other factors, such as cell design and resistance, exact solution composition, temperature, et cetera, are also specified. This practice has long tended to obscure the fundamental fact that the electrode potential, and not current density, is the conditio sine qua non which more often than not determines the success or failure of electrolytic methods; the current density cannot be adjusted arbitrarily to produce a desired rate of electrolysis without regard to the electrode potential. The importance of the electrode potential has, of course, long been recognized, but a preliminary determination of its optimum value in any given case has been difficult and often practically impossible by classical procedures, except for those rather rare instances which involve reversible oxidation-reduction reactions accessible to the ordinary potentiometric methods.[2]

The purpose of the present paper is to demonstrate the extent to which electrolytic preparative

procedures can be rationalized and improved by using the polarographic method of electrolysis[3] as a pilot technique to establish optimum electrolysis conditions before actual preparative work is undertaken. The term "polarographic synthesis" is suggested to describe this new technique.

From a preliminary polarographic investigation of a projected starting material under widely diverse conditions of solution composition, pH, temperature, et cetera, the feasibility of, and optimum conditions for, a large-scale electrolytic preparation with practically quantitative yield usually can be determined readily, regardless of whether or not the electrode reaction is reversible. Since the polarographic method need not be limited to the dropping mercury electrode, but can also be applied to solid microelectrodes,[3] it may also serve to determine the most satisfactory electrode material for a given reaction; this should prove to be especially advantageous in investigating selective oxidation reactions at a large platinum anode of alcohols, acids (Kolbe synthesis), hydrocarbon side chains (controlled stepwise degradations), etc. Furthermore, information obtained in a preliminary polarographic investigation should be a valuable aid in solving the frequent and often difficult problem of selecting the proper "chemical" reducing or oxidizing agent for effecting a desired reaction, particularly in those cases where the reduction or oxidation proceeds through several stages.

The present study is concerned chiefly with the application of the proposed method to the preparation of 9-(o-iodophenyl)-dihydroacridine by reduction of 9-(o-iodophenyl)-acridine according to

(1) National Scholar, Harvard University, 1942–43.

(2) For a comprehensive review of the organic electrochemical preparative literature, see S. Glasstone and A. Hickling, "Electrolytic Oxidation and Reduction," D. Van Nostrand Co., New York, N. Y., 1936.

(3) I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1941.

$$+ 2H^+ + 2e \longrightarrow \qquad (1)$$

I   H II
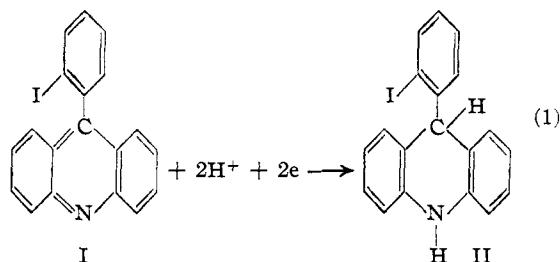
This reaction was chosen as a test case because compound II was desired for another purpose, because it presents about as many difficulties as are likely to be encountered with other reactions, and because all chemical reducing agents that were tried (before polarographic information was obtained) either did not effect reduction of I or else led to complete reduction of II with elimination of iodine.

Experimental

9-Phenylacridine was prepared by the method of Bernthsen,[4] with recrystallization from toluene and then from alcohol (m. p. 181–183°, cor.).

9-(o-Iodophenyl)-acridine, a compound not previously reported, was prepared in an analogous way by heating diphenylamine with excess o-iodobenzoic acid in molten zinc chloride as a solvent at 230–265° for six hours, extracting with alcohol, precipitating with concentrated aqueous ammonia, and repeatedly recrystallizing from chloroform. The product consisted of yellow crystals which melted with decomposition at 264-268°.

Anal. Calcd. for $C_{19}H_{12}NI$: C, 59.9; H, 3.18; I, 33.2. Found: C, 60.3; H, 3.30; I, 32.8.

Apparatus.—The usual polarographic technique was employed,[3] most of the polarograms being determined with a simple manual apparatus that has already been described.[3,5] An H-type polarographic cell, with a saturated calomel working reference electrode, and a dropping electrode assembly similar to that described by Lingane and Laitinen,[6] were used. Air was removed from the solutions with nitrogen, and polarograms were obtained at 25°.

After experimenting with various types of cells for preparative work at a controlled potential, the design shown in Fig. 1 was finally found to be most convenient and satisfactory. It includes the required features of reasonably low resistance (ca. 180 ohms with electrolyte concentrations of the order of 0.5 M), minimum interdiffusion of the catholyte and anolyte, and provision for removing dissolved air from both compartments. Removal of dissolved air may not always be necessary, but it was an essential precaution in the present case because the reduction products are rather easily air-oxidized. Furthermore, oxygen is reduced at a mercury cathode[3] and removal of air is necessary if the current efficiency is to be determined by integration of the current–time curve obtained in an elec-
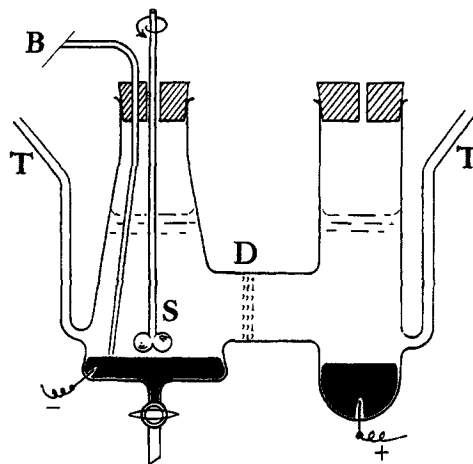
(4) A. Bernthsen, *Ann.*, **224**, 12 (1884).

(5) J. J. Lingane and I. M. Kolthoff, THIS JOURNAL, **61**, 825 (1939).

(6) J. J. Lingane and H. A. Laitinen, *Ind. Eng. Chem., Anal. Ed.*, **11**, 504 (1939).

Fig. 1.—Cell for electrolytic preparations at controlled potential.

trolysis. At potentials between about −0.3 and −0.9 v. *vs.* the S. C. E. hydrogen peroxide is the reduction product of oxygen at a mercury cathode, and obviously its presence may lead to undesirable side reactions in certain instances.

The large compartment was constructed from a 500-cc. wide-mouthed Erlenmeyer flask. A coarse sintered glass disk, D, 4 cm. in diameter, is sealed into the connecting tube between the two compartments to minimize interdiffusion of the two solutions. Both compartments are provided with gas inlet tubes T for removal of dissolved air with a stream of nitrogen.

In the experiments described below a large pool of mercury on the bottom of the larger compartment (area *ca.* 68 sq. cm.) was used as the working electrode (cathode), and a similar pool of mercury (area *ca.* 20 sq. cm.) on the bottom of the smaller compartment served as auxiliary electrode (anode). With the exception of the substance to be reduced, both compartments contained the same solution. With the alkaline supporting electrolyte used the reaction at the anode was the oxidation of mercury to mercuric oxide; the latter was formed in a loose layer which in no way interfered with the passage of current, and since the current density never exceeded about 0.01 amp./sq. cm., the anode potential remained quite constant. For cases in which the presence of oxygen is not objectionable a large platinum or carbon anode can also be used with satisfactory results.

To provide the efficient stirring which is essential to proper control of the potential of the working electrode, a propeller-type glass stirrer S was mounted in the cathode compartment close to the mercury surface, and it was rotated in the direction which impelled solution against the electrode. The magnitude of the current was greatly dependent on the rate of stirring, which was to be expected, because the rate of stirring determines the thickness of the diffusion layer at the electrode.

The potential of the large mercury cathode was measured against a saturated calomel reference electrode with a potentiometer in the usual way, and it was controlled by varying the total e. m. f. applied to the cell. A narrow U-tube, B, filled with saturated potassium chloride in a

3% agar gel, served as a salt bridge between the saturated calomel reference electrode and the mercury cathode; the tip of this bridge was placed very close to the mercury surface (within 1 mm.) to minimize the amount of ohmic potential drop in the solution that is included in the measured cathode potential. From experiments in which the separation of the salt bridge tip and the mercury cathode was varied, it was found that this iR drop did not introduce an uncertainty of more than ±0.01 v. in the measured cathode potential if the tip of the bridge was about 1 mm. from the electrode surface. The total e. m. f. applied to the cell was taken from the d. c. house main, and it was regulated with a rough potentiometer-rheostat to maintain the measured cathode potential at the desired value. In routine work it would be advantageous to provide some sort of device which would automatically adjust (decrease) the applied voltage to maintain the cathode potential at a desired constant value.

A calibrated ammeter was included in the circuit to measure the current through the cell.

Results and Discussion

The polarographic characteristics of 9-phenyl-acridine and 9-(o-iodophenyl)-acridine in various media were first determined. In aqueous 0.1 N hydrochloric acid the waves of both compounds show maxima that are not easily eliminated by gelatin, but in the presence of 50–90% ethanol the maxima are completely eliminated and the waves and diffusion currents are well defined.

In 0.01 to 1 N hydrochloric acid in 50% ethanol phenylacridine produces a double wave with half-wave potentials at -0.61 v. and -0.72 v. $vs.$ the S. C. E. The *relative* height of the first wave decreased very markedly with increasing concentration of hydrochloric acid, but the total diffusion current (sum of both waves) was virtually unaffected by the acid concentration. With a constant concentration of hydrochloric acid (0.2 N) in 50% ethanol, the ratio of the first to second wave heights, i_1/i_2, decreased from 4.7 to 0.14 as the concentration of phenylacridine was increased from 0.385 to 3.17 millimolar, and the ratio $(i_1 + i_2)/Cm^{2/3}t^{1/6}$ increased from 1.17 to 1.81 microamp./millimole/liter/mg.$^{2/3}$ sec.$^{-1/2}$ at 25°. It seems evident from these results that the double wave is not due to reduction of the phenylacridine in separate stages of different electron equivalents, but must be due to some other cause. From results described below we believe that the formation of a slightly soluble dimer of phenyl- and dihydrophenyl acridines is responsible for the double wave.

The iodophenylacridine in 0.1 N hydrochloric acid in 50% ethanol produced only a single well-defined wave whose half-wave potential was -0.59 v. $vs.$ the S. C. E., and hence practically the same as that of the phenylacridine. In this case $i_d/Cm^{2/3}t^{1/6}$ was constant and equal to 1.56, with the same capillary and experimental conditions as in the case of phenylacridine above. In spite of the variation with concentration of i_d/C of phenylacridine, it is evident from these data that the electron requirement must be the same in the reduction of both compounds, and, since there is no doubt that the phenylacridine is reduced to 9-phenyl-dihydroacridine, it follows that the iodophenylacridine must be reduced to 9-(o-iodophenyl)-dihydroacridine under these conditions *without loss of iodine* (reaction 1 above).

In 0.1 M tetramethylammonium hydroxide in 50% ethanol the phenylacridine produced a well-defined wave with a half-wave potential of -1.20 v. $vs.$ the S. C. E., and a value of $i_d/Cm^{2/3}t^{1/6}$ of 1.77 at 25°. Under the same conditions the iodophenylacridine produced a poorly separated double wave with half-wave potentials of -1.21 and -1.33 v., but the total diffusion current was well defined and $i_d/Cm^{2/3}t^{1/6}$ was equal to 3.44. This is very nearly twice the value of i_d/C observed with the phenylacridine, and therefore it is evident that under these conditions the *iodo* compound undergoes a 4-electron reduction with elimination of iodine. Since the half-wave potential for the first part of the double wave of iodophenylacridine is practically identical with that of phenylacridine, it was concluded that the first part of the wave corresponds to hydrogenation according to reaction 1 above and the second part to the further reduction of the 9-(o-iodophenyl)-dihydroacridine with elimination of iodine. The correctness of this conclusion was verified in the preparative experiments described below.

In 0.1 N potassium hydroxide containing 0.5 N potassium acetate as additional supporting electrolyte in 50–90% ethanol, the separation of the two waves of iodophenylacridine is much improved, as shown in Fig. 2, the half-wave potentials being -1.32 and -1.62 v. $vs.$ the S. C. E.

From the above data an acid supporting electrolyte would normally be chosen to prepare the 9-(o-iodophenyl)-dihydroacridine, (II), both from the standpoint of greater solubility in acid medium, and absence of the second stage of reduction before hydrogen evolution which permits a relatively large latitude in the choice of the cathode potential. However, for the present purpose of proving that either one or two stages of reduc-
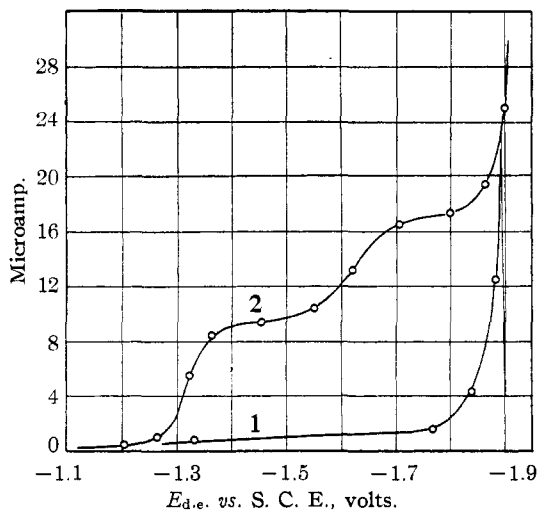
Fig. 2.—Polarogram, obtained with the dropping mercury electrode, of 2.22 × 10⁻³ M o-iodophenylacridine in 0.1 M potassium hydroxide and 0.5 M potassium acetate in 90% ethanol at 25° (Curve 2). Curve 1 is the residual current curve of the supporting electrolyte alone. $m^{2/3}t^{1/6} = 1.39\ mg.^{1/3}sec.^{-1/2}$.

tion can be obtained by proper control of the potential when a double wave exists, the preparative reductions were carried out in 0.1 N potassium hydroxide in 90% ethanol.

In a typical experiment a solution containing 0.803 g. (0.00210 mole) of o-iodophenylacridine in about 500 cc. of 0.1 N potassium hydroxide, and 0.5 N potassium acetate in 90% ethanol, was freed from air with nitrogen and reduced in the cell of Fig. 1 with the potential of the large mercury cathode maintained at −1.36 to −1.39 v. vs. the S. C. E. This potential corresponds to that at which the first diffusion current plateau is just reached on the polarograms obtained with the dropping electrode (compare Fig. 2), and it is well in advance of the beginning of the second stage of reduction. The current–time curve for this experiment is shown in Fig. 3. At the start the cathode potential was set at −1.36 v. and during the first fifty minutes it gradually increased to −1.39 v.; thereafter it was maintained between −1.38 and −1.39 v. by periodically decreasing the total e. m. f. applied to the cell. The current, after the first fifty minutes, decreased exponentially with time and became practically zero, as expected, after about one hundred twenty minutes.

By graphical integration of the curve in Fig. 3 the current consumption (corrected for the small residual current) was 42.3 coulombs, compared
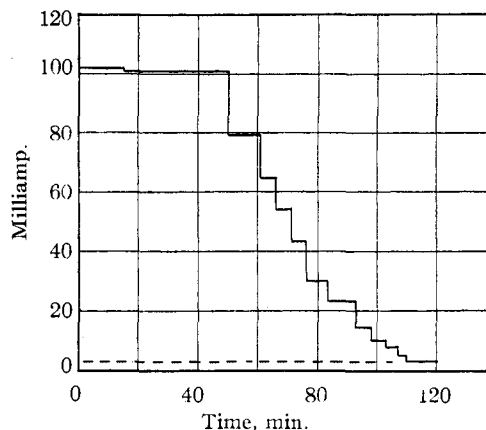

Fig. 3.—Current–time curve obtained in reduction of 0.803 g. (0.0021 mole) of o-iodophenylacridine from ca. 500 cc. of air-free 0.1 M potassium hydroxide in 90% ethanol in cell of Fig. 1. Cathode potential, −1.36 to −1.39 v. vs. S. C. E. Horizontal dashed line is the residual current (3 milliamp.).

with the theoretical value 0.00210 × 2 × 96,500 = 40.5 coulombs. The agreement is probably within experimental error, and it demonstrates that the current efficiency is virtually 100%. Similar results were obtained in other experiments.

The reduced solutions obtained under the above conditions were diluted with water and extracted repeatedly with chloroform in an atmosphere of nitrogen, the chloroform extracts were washed with water, filtered and evaporated to dryness under reduced pressure in nitrogen. The resulting crystalline product melted at 152–153° (cor.), and analysis showed 31.5% iodine compared with the theoretical value of 33.0% for 9-(o-iodophenyl)-dihydroacridine. In several experiments an average yield of 90% was obtained, which illustrates the high yield that can be expected in other cases. It was found that the product was easily oxidized back quantitatively to iodophenylacridine (characterized by color and high decomposition point) when its solution in methanol was warmed with silver oxide, but the dry material is stable in the air. As far as we are aware this is the first time that this substance has been prepared.

As expected, the current–cathode potential curves obtained with the large mercury cathode and well-stirred solution do not show the limiting currents that characterize the dropping electrode polarograms. The occurrence of a limiting diffusion-controlled current depends on the attainment of an extreme state of concentration polarization at the electrode surface,[3] whereas the condi-

tions extant with the large mercury electrode reduce concentration polarization to a minimum. This effect is demonstrated by the typical current–cathode potential curve in Fig. 4, which was obtained with a partially reduced solution of iodophenylacridine, and which shows only a slight suggestion of an inflection point. When the current is plotted against the *total* e. m. f. applied to the cell, instead of the cathode potential, there is no indication at all of a point of inflection or of successive electrode reactions, and the slope of the curve depends simply on the cell resistance. The curve in Fig. 4 is a good illustration of the difficulty that one encounters when an attempt is made to establish optimum potential conditions from current–voltage curves according to the classical method, and a comparison with the dropping electrode polarogram in Fig. 2 emphasizes the advantages of the polarographic pilot technique.
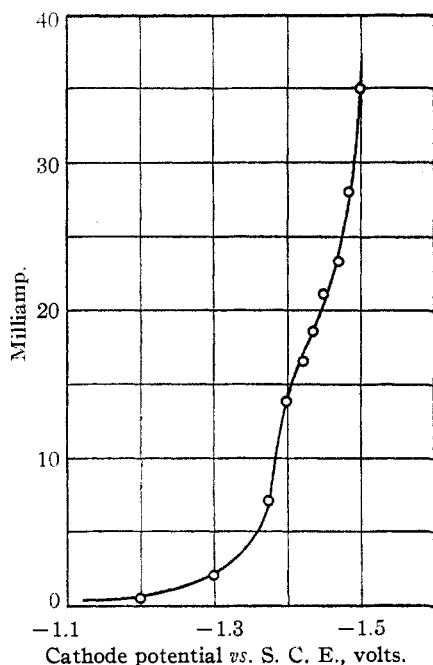

Fig. 4.—Current–cathode potential curve of an air-free partially reduced solution of *o*-iodophenylacridine in 0.1 *M* potassium hydroxide in 90% ethanol, obtained with cell of Fig. 1.

Further experiments have been performed in which solutions of iodophenyldihydroacridine prepared by reduction at −1.38 v. as described above, were further reduced with elimination of iodine by changing the cathode potential to −1.70 ± 0.02 v. (compare Fig. 2). The current–time curves in these experiments corresponded

to a current consumption that was equal, within an experimental error of about ±5%, with that previously obtained during the first stage of reduction. Extraction of the completely reduced solutions with chloroform as described above produced a 95% yield of pure phenyldihydroacridine, which was characterized by melting point (164–170°) and mixed melting point (163–170°) with an authentic pure sample of phenyldihydroacridine (m. p. 169–172°). To further confirm the identity of the phenyldihydroacridine, a sample was oxidized back with silver oxide in methanol solution; evaporation of the solution yielded a product that proved to be pure phenylacridine (m. p. 181–183°, cor.).

We wish to emphasize that caution must be observed in predicting from polarographic data alone the products that will be obtained in a large-scale electrolysis, because occasionally secondary reactions lead to a different product than that expected. For example, the polarographic technique is capable of determining the electron requirements of reactions involving the formation of free radicals or semiquinones, but the product actually obtained in a large-scale reduction may be a polymer of the expected product. A pertinent case is encountered in the reduction of phenyl acridine in acid medium. In a typical experiment a 0.0078 *M* solution of phenylacridine in 1 *N* hydrochloric acid in 50% ethanol was freed from air with nitrogen and reduced according to the above technique with the potential of the large mercury cathode maintained at −0.85 v. *vs.* the S. C. E., corresponding to a potential well onto the limiting current plateau of the wave obtained with the dropping electrode. The originally yellow solution decolorized and a heavy crimson precipitate deposited as the electrolysis proceeded. The current–time curve corresponded to a current consumption about 30% greater than that expected for a 1-electron reduction. The bright red color of the dried precipitate slowly reverted to the characteristic yellow color of phenylacridine after a few days in air. When attempts were made to recrystallize the red product by dissolving it in a little 95% ethanol and reprecipitating with water, a very light lemon-colored precipitate was obtained, which was very probably a mixture of phenyl- and dihydrophenylacridine. These facts, *i. e.*, intense color, very slight solubility, nearly 1-electron current consumption in the reduction, and apparent disproportionation on

recrystallization, constitute fairly convincing evidence that the red product was a dimer of phenylacridine and dihydrophenylacridine. The formation of this substance may account for the peculiar double wave that was observed on the polarograms of phenylacridine in strongly acid medium, and the inconstancy of i_d/C, already mentioned, and this possibility is being further investigated.

The amounts of material prepared in the above experiments were limited to the order of a gram or less because the starting materials were fairly difficult to prepare and were available in only small amounts, but there is no evident reason why the method could not be applied to much larger scale preparations. Furthermore, the method need not be limited to the use of mercury working electrodes, but probably can also be applied with solid electrodes if the preliminary polarographic investigation is performed with microelectrodes of the same material.

Summary

The polarographic method has proved to be a valuable and convenient pilot technique to establish optimum conditions for carrying out electrolytic preparations at a controlled potential. In the present investigation this method of "polarographic synthesis" has been applied chiefly to the reduction of 9-(o-iodophenyl)-acridine, which served as a good test case because the reduction proceeds in two stages, first to 9-(o-iodophenyl)-dihydroacridine (I) and then to 9-phenyldihydroacridine (II) with elimination of iodine, and the reduction potentials of the two stages are separated by only about 0.3 v. at a mercury cathode. A cell and procedure have been described with which it was easily possible to prepare either compound I or II in a high state of purity, and with practically quantitative yield, by proper control of the potential of a working mercury cathode. From the experience gained thus far it appears that this method is capable of wide application in organic chemistry, and it should be particularly valuable whenever a selective oxidation or reduction of only one of two approximately equally reactive structures in a molecule is required.

The Activity and Osmotic Coefficients of Sodium Chlorate by an Isopiestic Method

BY JAMES HOMER JONES

The activity coefficients of sodium chlorate in aqueous solution at concentrations up to one molal have been determined by Scatchard[1] and co-workers from freezing point measurements. This investigation was undertaken to obtain the activity coefficients at 25° and to extend the experimentally determined activity coefficients to higher concentrations.

Experimental

Method and Apparatus.—The method employed was the isopiestic method, using an apparatus similar to that described by Phillips, Watson and Felsing.[2] The procedure was similar except that only six cups were employed at one time so that the time required to attain equilibrium would be shortened. Sodium chloride was chosen as the reference salt.

Purification of Materials: Sodium Chloride.—Reagent grade sodium chloride was dissolved in conductivity water and precipitated by hydrogen chloride gas. The salt was recrystallized from conductivity water, dried in

platinum dishes at 300-400° and powdered in an agate mortar. The salt was stored in a vacuum desiccator over solid potassium hydroxide.

Sodium Chlorate.—Reagent grade sodium chlorate was recrystallized three times from conductivity water. The salt was partially dried at 100° in an oven. The lumps were broken up in an agate mortar and the salt finally dried in a vacuum desiccator at 100° with solid potassium hydroxide as desiccant.

Preparation of Solutions.—The dry salts were weighed by difference from weighing bottles into 125-ml. glass-stoppered Erlenmeyer flasks, and the calculated amount of water added. Frequent checks of concentration were made by evaporation of solution with concentrated sulfuric acid, igniting and weighing as sodium sulfate.

The solutions were weighed by difference into the weighed cups from weight burets. Samples ranged from 2.0 to 3.5 g. The precision in weighing was better than one part in 4000 for samples of two grams.

In order to test the apparatus, the isopiestic ratios of potassium chloride–sodium chloride were determined simultaneously with the sodium chloride–sodium chlorate ratios. The results agree within experimental error with the results of both Felsing[2] and Robinson.[3]

(1) Scatchard, Prentiss and Jones, THIS JOURNAL, **56**, 805 (1934).

(2) Phillips, Watson and Felsing, *ibid.*, **64**, 244 (1942).

(3) Robinson, *Trans. Faraday Soc.*, **35**, 1217 (1939).