Summary

A number of dialkylaminoalkyl and dialkyl-aminoalkoxyalkyl esters of amino-1- and amino-2-naphthoic acid as well as dialkylaminoalkylamides

of amino-1-naphthoic acid have been described.

The amides seem to be much less satisfactory as local anesthetics than the esters.

The Introduction of Substituted Vinyl Groups. VI. The Regeneration of Substituted Vinyl Malonic Esters from their Sodium Enolates[1]

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The alkylation of sodium enolates prepared from alkylidene malonic and cyanoacetic esters affords a rather general method for preparing substituted vinyl *alkyl* malonic and cyanoacetic esters.[2] While the alkyl group introduced on
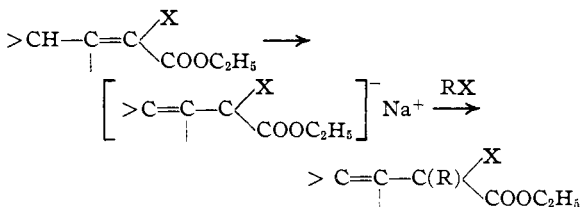
$$X = CN \text{ or } COOC_2H_5$$

the α carbon atom locks the double bond in the β,γ-position, a similar introduction of hydrogen would give an ester capable of isomerizing to the original α,β-unsaturated ester by a simple prototropic shift.

Kon and his associates[3] have developed a technique for regenerating esters containing a mobile three-carbon system from their sodium or potassium enolates, in which petroleum ether suspensions of the enolates are treated with a weak organic acid. Under these non-polar conditions enol–keto change occurs, but in many cases three-carbon tautomerism is arrested or retarded, so that the labile esters corresponding in structure to the metal enolates can be isolated. This procedure was applied[4] to one alkylidene malonic ester, ethyl cyclopentylidenemalonate, I. The ester regenerated from the sodium or potassium enolate prepared from I had but a small exaltation in molecular refraction, and a high additive capacity for iodine chloride, indicating that it was largely

ethyl 1-cyclopentenyl malonate, II. Accurate
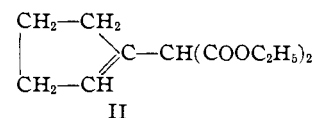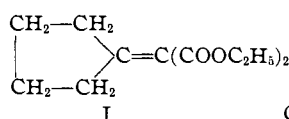
analysis of the regenerated ester by the iodine chloride addition method was not possible, but the molecular refraction data indicated that it contained at least 82% of II.

The reaction of secondary alkylidene malonic esters with sodamide in liquid ammonia[5] now affords a more satisfactory method for preparing sodium enolates from such esters than was available at the time of Kon's work. We have regenerated the labile esters from the sodium enolates prepared from the three readily available esters of this type: *i. e.*, ethyl isopropylidenemalonate, ethyl cyclopentylidenemalonate and ethyl 1-methylpropylidenemalonate. It has been found possible to determine the purity of the regenerated esters fairly accurately by the method of polarographic analysis.

Treatment of an ether suspension of the sodium enolate prepared from ethyl isopropylidenemalonate with benzoic acid, acetic acid, dilute hydrochloric acid or water gave samples of ethyl isopropenylmalonate of approximately equal purity. The three carbon system of the ester is sufficiently immobile to resist isomerization by cold dilute acids and bases. Decomposition of ether suspensions of the sodium enolates prepared from the three alkylidene malonic esters with dilute hydrochloric acid was consequently employed in preparing the β,γ-unsaturated esters whose properties are listed in Table I. The prop-

(1) Supported by a grant from the Penrose Fund of the American Philosophical Society.

(2) THIS JOURNAL, **62**, 314 (1940), and preceding papers in this series.

(3) Kon and Nanji, *J. Chem. Soc.*, 560 (1931); Gidvani, Kon and Wright, *ibid.*, 1027 (1932).

(4) Kon and Ling, *ibid.*, 596 (1934); Hugh and Kon, *ibid.*, 778 (1930).

(5) Cope and Hancock, THIS JOURNAL, **60**, 2644, 2901 (1938).

Table I

Ester, ethyl—malonate	Unsaturation	B. p., °C. (uncor.)	Mm.	$n^{25}D$	d^{25}_{25}	Molecular refraction Calcd.	Found	Exaltation
Isopropylidene	α,β	111–113	9	1.4478	1.0254	51.23	52.42	+1.19
Isopropenyl	β,γ (98.4%)	105–106	12	1.4331	1.0156	51.23	51.37	0.14
1-Methyl propylidene	α,β	119.5–120.5	10	1.4479	1.0108	55.85	56.86	1.01
1-Methyl propenyl	β,γ (97%)	116–117	10	1.4372	1.0053	55.85	56.00	0.15
Cyclopentylidene	α,β	142–143	10	1.4707	1.0630	58.27	59.63	1.36
1-Cyclopentenyl	β,γ (97%)	147–148	17	1.4566	1.0551	58.27	58.49	0.22

erties of the original alkylidene esters are also recorded for comparison.

The extent to which the β,γ-unsaturated malonic esters are contaminated by the α,β-unsaturated esters from which they are prepared cannot be determined by iodometric titration[6]
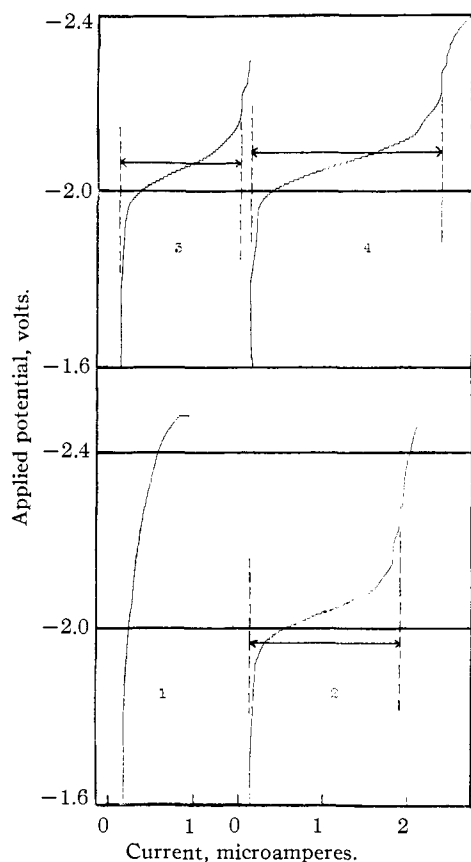

Fig. 1.—Photographs of typical curves obtained in the polarographic analyses, showing the waves due to reduction of the α,β-unsaturated esters. The small waves present in curves 2 and 4 at a high applied potential were characteristic of the respective α,β-unsaturated esters, whether in the pure state or present as impurities in small amount in the β,γ-unsaturated esters. The total waves were therefore measured as indicated: (1) 0.02 M tetramethylammonium chloride in 76% ethyl alcohol. (2) 1.03 × 10⁻³ M ethyl isopropylidenemalonate. (3) 1.03 × 10⁻³ M ethyl 1-methylpropylidenemalonate. (4) 1.04 × 10⁻³ M ethyl cyclopentylidenemalonate.

(6) Linstead, et. al., J. Chem. Soc., 355, 2565 (1927); 723 (1931).

because of the slowness with which they add iodine chloride. It was possible to apply polarographic analysis to determine the purity of the regenerated esters because the α,β-unsaturated esters were reduced at the dropping mercury electrode, but the β,γ-unsaturated isomers were not.[7] The α,β-unsaturated esters reduced at rather high potentials, giving waves (Fig. 1) proportional in height to the concentration of the esters. By comparing the heights of the waves given by standard solutions of the pure α,β-unsaturated esters and the regenerated esters described in Table I the latter were found to contain 1.6, 3.0 and 3.0% of the α,β-unsaturated esters, respectively.
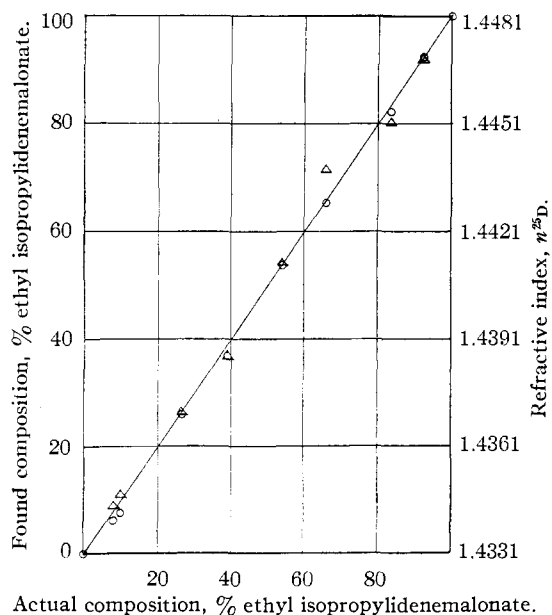

Fig. 2.—Analysis of known mixtures of ethyl isopropylidene and isopropenyl malonates: △, plot of composition determined by polarographic analysis against actual composition; ○, plot of refractive index against composition. Deviations from the ideal line are a measure of the experimental error.

The accuracy of the polarographic method in analyzing mixtures of ethyl isopropenyl and iso-

(7) This was anticipated since Schwaer has shown that unsaturated organic acids are reducible only when the double bonds are conjugated; cf. Müller, Chem. Rev., 24, 110 (1939).

propylidene malonates was tested by analyzing known mixtures of the isomers. The results are shown graphically in Fig. 2, which also contains refractive index data for the mixtures. The average and maximum deviations between the calculated and found ratios of the pair of isomers were 1.8 and 5%. The method should be of value in analyzing other similar pairs of isomers in cases where the pure α,β-unsaturated forms can be isolated. It supplements in this respect the iodometric and bromometric methods developed by Linstead,[6] which are most accurate in cases where the pure β,γ-unsaturated isomers can be isolated.

While both the α,β- and β,γ-unsaturated malonic esters react rapidly with sodium ethoxide, and presumably equilibrium between the pairs of isomers could be established with sodium ethoxide as a catalyst, it seemed of interest to attempt to establish equilibrium in the absence of reagents capable of combining selectively with either form. Trial showed that the isomers are stable at 180°, but that they are isomerized by heating in the presence of hydrogenation catalysts at that temperature. Each of the six unsaturated compounds was heated at 180° in the presence of Raney nickel in a nitrogen atmosphere until additional heating produced no further change in refractive index. The compounds were then distilled without fractionation and subjected to polarographic analysis. Ethyl isopropylidene and isopropenyl malonates reached an equilibrium containing 98% (within experimental error of 100%) of the α,β-unsaturated ester, while ethyl cyclopentylidene and 1-cyclopentenyl malonates reached an equilibrium containing 63% of the α,β-unsaturated form. Ethyl 1-methylpropenylmalonate was rearranged to ethyl 1-methylpropylidenemalonate to the extent of at least 86% under these conditions, but the exact position of equilibrium could not be established.

It is of interest to note in comparison with the equilibrium value found for ethyl cyclopentylidene and 1-cyclopentenyl malonates that Kon and Speight[8] have reported that the product obtained from cyclohexanone and ethyl malonate is the pure β,γ-unsaturated ester, ethyl 1-cyclohexenyl malonate.

Experimental Part

Ethyl isopropylidenemalonate and ethyl 1-methylpropylidenemalonate prepared by condensing acetone and

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(8) Kon and Speight, *J. Chem. Soc.*, 2727 (1926).

methyl ethyl ketone with malonic ester[5] had constant boiling points and refractive indexes, indicating the absence of the β,γ-unsaturated isomers. The product obtained from cyclopentanone and malonic ester by the method of Hugh and Kon[4] was a mixture of the α,β- and β,γ-unsaturated isomers. Fractionation of the mixture through a Fenske type column with a 70 × 1.2 cm. section packed with glass helices was employed to purify the higher boiling ethyl cyclopentylidenemalonate[9] (properties in Table I).

Preparation and Properties of the β,γ-Unsaturated Esters. Ethyl Isopropenylmalonate.—The sodium enolate was prepared from 50 g. (0.25 mole) of ethyl isopropylidenemalonate and the sodamide from 6.32 g. (0.275 mole) of sodium in liquid ammonia by the procedure previously described.[5] After stirring the liquid ammonia solution for ten minutes, 300 cc. of dry ether was added and the mixture was stirred and warmed until most of the ammonia had evaporated. The last traces were distilled out with a little of the ether. The suspension of the enolate in ether was cooled in ice and 26 cc. of 36% hydrochloric acid (0.30 mole) in 200 cc. of ice water was added rapidly. The mixture was stirred vigorously for five minutes. The ether layer was separated and the aqueous layer extracted with benzene. The combined ether and benzene solutions of the ester were washed with dilute sodium bicarbonate solution and water, the solvent removed and the product distilled in vacuum through a Widmer column. The yield of ethyl isopropenyl malonate (Table I) was 44 g.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.11; H, 8.18.

In preparations otherwise similar to the above the sodium enolate was decomposed with: an equivalent quantity of benzoic acid in dry ether; an equivalent quantity and 10% excess of anhydrous acetic acid; water. The samples of ethyl isopropenylmalonate obtained in these preparations varied in refractive index from 1.4331 to 1.4342.

Several unsuccessful attempts were made to obtain ethyl isopropenylmalonate by acidification of the sodium enolate prepared in absolute alcohol. Solutions of the sodium enolate prepared as in ref. 5, procedure C, which were at −5°, were treated with: an equivalent quantity of hydrochloric acid in 175 cc. of ice water; the same after 100 cc. of benzene had been added to extract the ester as it was formed; a 10% excess of anhydrous acetic acid. In each case the ester was separated by extraction, washed and distilled as described above. The product obtained by the second of these procedures had n^{25}D 1.4443, indicating that it contained about 24% of ethyl isopropenylmalonate. The first and last procedures gave material which did not differ significantly in refractive index from ethyl isopropylidenemalonate.

Several experiments were carried out to determine whether ethyl isopropenylmalonate would be stable under conditions more drastic than those existing during its preparation and purification. Samples of the ester were recovered unchanged after shaking for two hours with 0.1 N hydrochloric acid and sodium hydroxide at room

(9) Kon (ref. 4) purified this ester by saponifying the mixture of α,β- and β,γ-unsaturated esters to obtain pure cyclopentylidenemalonic acid, which was then esterified through the silver salt.

temperature, and after refluxing for thirty minutes at atmospheric pressure (temperature of the liquid 222°). Alcoholic sodium ethoxide isomerized ethyl isopropenylmalonate rapidly. The ester (11.2 g.) was refluxed for thirty minutes with a solution of 0.13 g. of sodium (0.1 equivalent) in 50 cc. of absolute alcohol. The solution was cooled and poured into ice water containing enough hydrochloric acid to neutralize the sodium hydroxide formed. The ester was extracted with ether and distilled. It weighed 9.4 g. and had n^{25}D 1.4474, indicating an ethyl isopropylidenemalonate content of about 97%.

The fact that ethyl isopropenylmalonate is rearranged in the presence of bases prevented its transformation into a solid derivative. The ester (4 g.) on shaking with 25 cc. of concentrated ammonia for twenty-four hours gave 1.2 g. of malonamide, the product which is formed from ethyl isopropylidenemalonate[10] under these conditions. Hydrolysis of the ethyl isopropenylmalonate by refluxing with aqueous barium hydroxide was accompanied by isomerization, for the product obtained on acidification and extraction with ether was isopropylidenemalonic acid. Hydrolysis under milder conditions was accomplished by treating the ester (4 g.) with 48 cc. of 5% alcoholic sodium hydroxide at room temperature. A sodium salt started to separate after a few minutes. The mixture was filtered after standing overnight, and the sodium salt (3.6 g.) washed with alcohol and ether. One gram of the sodium salt in 11 cc. of water was refluxed for thirty minutes with a solution of 2.3 g. of p-nitrobenzyl bromide in 22 cc. of alcohol. The crude p-nitrobenzyl ester which separated on cooling was recrystallized from dilute alcohol; yield 0.5 g., m. p. 119.5–120.5°. The same ester was obtained in a similar preparation from ethyl isopropylidenemalonate, and the derivative is therefore the di-p-nitrobenzyl ester of isopropylidenemalonic acid.

Anal. Calcd. for $C_{20}H_{18}O_8N_2$: N, 6.76. Found: N, 6.62.

Ethyl 1-Methylpropenylmalonate.—By the sodamide–dilute hydrochloric acid procedure described above 53.5 g. of ethyl 1-methylpropylidenemalonate gave 43 g. of ethyl 1-methylpropenylmalonate (Table I).

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.53; H, 8.57.

Ozonization of the ester in chloroform solution, followed by decomposition of the ozonide in the usual manner[5] produced acetaldehyde, identified by the m. p. and mixed m. p. of the 2,4-dinitrophenylhydrazone. Color tests for formaldehyde were very weak. The ester therefore contains the 1-methyl propenyl rather than the 1-ethyl vinyl group.

Ethyl 1-Cyclopentenylmalonate.—In the same manner 56.5 g. of ethyl cyclopentylidenemalonate yielded 40 g. of ethyl cyclopentenylmalonate (Table I).

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.63; H, 8.02.

In all of the above preparations the esters were separated into three fractions on distillation. The refractive index of the last fraction was always higher than that of the middle fraction, usually by 0.0002 to 0.0020 unit, indicating slight contamination by the α,β-unsaturated esters which

were present in larger quantity in the higher boiling fractions. The data in Table I were obtained on the middle fractions.

Isomerization in the Presence of Hydrogenation Catalysts.—Although ethyl isopropenylmalonate was recovered unchanged after refluxing for twenty-four hours with palladinized charcoal in alcohol solution, the index of refraction of samples of the ester which were heated with palladinized charcoal and Raney nickel at 180° for two hours increased to 1.4398 and 1.4438, respectively. Approximately 25-g. samples of each of the six esters in Table I were heated at 180° in the presence of 1 g. of Raney nickel catalyst in a nitrogen atmosphere for five to six hours and distilled in vacuum through a small Widmer column, without fractionation after removing 0.5 to 2.0 g. of the monocarboxylic ester which was formed in each case. The esters were again heated with Raney nickel for one hour and redistilled, the process being repeated until the refractive index of the product remained constant. The isomerizations were complete after five to seven hours. The isomerized esters were analyzed by means of the polarograph with the following results. Content of α,β-unsaturated ester after heating: ethyl isopropenylmalonate, 98.4%; ethyl isopropylidenemalonate, 98.8%; ethyl 1-cyclopentenylmalonate, 63.5%; ethyl cyclopentylidenemalonate, 62.6%; ethyl 1-methylpropenylmalonate, 86%; ethyl 1-methylpropylidenemalonate, 111%. Obviously some by-product was formed when the last of the above esters was heated which interfered with the polarographic analysis. Quantitative reductions of the products of isomerization of each of the β,γ-unsaturated esters required within experimental error of one molar equivalent of hydrogen, proving that none of the changes in properties could be ascribed to partial saturation of the double bond.

Iodometric Analysis of Ethyl Isopropenylmalonate.—After several preliminary trials the method of Linstead and May[11] was followed, except that two molar equivalents of iodine chloride were used and the reaction time was greatly extended. Ten-cc. aliquots of standard carbon tetrachloride solutions of ethyl isopropenyl or isopropylidene malonates containing approximately 0.0007 mole of ester were treated with exactly twice the theoretical quantity of iodine chloride (prepared as by Linstead and May in twice the concentration which they employed). Blanks were prepared at the same time in which the same amount of iodine chloride was treated with 10 cc. of carbon tetrachloride. All of the samples were stored in the dark in glass stoppered bottles. After definite periods of time the amount of unchanged iodine chloride in each sample was determined. The additions were so slow that corrections for the decomposition of the iodine chloride (from the blank determinations) were very large; the reagent decomposed to the extent of 28 to 38% in 192 to 360 hours. The per cent. addition to ethyl isopropenylmalonate became roughly constant after 192 hours, and at 192, 240, 312 and 360 hours was 101.8, 108.1, 98.7 and 96.2%. The addition to ethyl isopropylidenemalonate after the same lengths of time was 14, 12, 15.2 and 12.5%. These results indicate that the former ester is largely β,γ-unsaturated, but they furnish no exact information concerning its purity.

(10) Kötz, *J. prakt. Chem.*, [2] **75**, 497 (1907).

(11) Linstead and May, *J. Chem. Soc.*, 2578 (1927).

Polarographic Analysis.[12]—A Leeds and Northrup Electrochemograph was used in the quantitative analyses. The principal difficulty was caused by the fact that the three α,β-unsaturated esters are reduced at high applied potentials, in the range of -1.9 to -2.2 volts. Tetramethylammonium chloride was used as the supporting electrolyte, since it is not reduced appreciably until even higher negative potentials. The analyses were carried out as follows. The instrument was used at one-tenth of full sensitivity, equivalent to a full-scale current range of 10 microamperes. The drop time of the mercury electrode was 3.9 seconds at -1.6 volts. All analyses were performed at $25 \pm 1°$ in an atmosphere of nitrogen. A 0.02 M solution of tetramethylammonium chloride[13] in 76% ethyl alcohol was prepared and analyzed in triplicate with the polarograph (representative curve 1, Fig. 1). Accurately weighed samples of the three α,β-unsaturated esters were dissolved in this solution to give solutions of known concentration, approximately 1×10^{-3} molar. These solutions were analyzed with the polarograph, curves, of which 2, 3 and 4 in Fig. 1 are representative, being obtained. These curves were made in triplicate, and the whole procedure was repeated with another known solution of each of the α,β-unsaturated esters. The distance between the lower vertical portion of each curve occurring before reduction started and a characteristic vertical portion of the curve occurring after reduction was complete was measured (see Fig. 1). The horizontal displacement of the curve given by the supporting electrolyte between the voltages at which the wave began and ended was measured and subtracted from the measured wave height, to give a "corrected wave height" due to reduction of the ester. For example, a 1.03×10^{-3} molar solution of ethyl isopropylidenemalonate gave waves of 43.4, 43.7 and 44.4 mm. The correction for reduction of the supporting electrolyte was 5.8 mm., making the corrected wave heights 37.6, 37.9 and 38.6 mm., or an average of 38.0 mm. For convenience this value was reduced to a height corresponding to a concentration of 1×10^{-3} molar; $38.0/1.03 = 36.9$ mm. for 1×10^{-3} molar. Another solution 1.08×10^{-3} molar gave corrected wave heights of

40.9, 39.9 and 40.1 mm. The average of these values over the concentration = $40.3/1.08 = 37.3$ mm. for 1×10^{-3} molar. The average of the two values, 37.1 mm., was used as a standard in analyzing the mixtures for ethyl isopropylidenemalonate. The amount of α,β-unsaturated ester present in each of the β,γ-unsaturated esters (Table I) was determined by measuring the waves given by the latter in a total concentration of approximately 2×10^{-2} molar. For example, a 1.92×10^{-2} molar solution of ethyl isopropenylmalonate gave an average corrected wave height of 11.2 mm., or $11.2/19.2 = 0.583$ mm. for 1×10^{-3} molar. The α,β-unsaturated ester content is therefore $0.583/37.1 \times 100 = 1.6\%$. The known mixtures for which analyses are recorded in Fig. 2 were analyzed in a similar manner, in solutions sufficiently concentrated to give waves from 10 to 30 mm. in height in most cases. The average corrected wave heights for 1×10^{-3} molar ethyl 1-methylpropylidenemalonate and ethyl cyclopentylidenemalonate were 31.6 and 46.2 mm., respectively. From the correspondence of duplicate analyses made by the above procedure, the error introduced into the determinations by variability of the instrument and latitude in choice of the proper portions of the curves for measurement was $\pm 2.5\%$ or less in almost every case. The "half-wave potentials" for all three of the α,β-unsaturated esters were between -2.03 and -2.06 volts (applied potential).

Summary

Decomposition of ether suspensions of the sodium enolates prepared from ethyl isopropylidene, 1-methylpropylidene and cyclopentylidene malonates with acids produces ethyl isopropenyl, 1-methylpropenyl and 1-cyclopentenyl malonates. The amount of the original α,β-unsaturated esters present in the β,γ-unsaturated isomers can be determined by means of polarographic analysis, a method which should be quite generally applicable to the analysis of such mixtures in cases where the pure α,β-unsaturated form can be isolated. The interconversion of these α,β- and β,γ-unsaturated isomers in the presence of Raney nickel has been studied.

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(12) We are indebted to Dr. George A. Perley and Mr. R. H. Cherry of the Leeds and Northrup Co., Philadelphia, for advice and assistance at the outset of this work.

(13) Purified by two or more recrystallizations from ethyl alcohol, until a sample gave a polarogram like curve 1 in Fig. 1, showing no waves indicating the presence of amine salts.