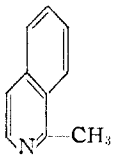
[Communication No. 1347 from the Kodak Research Laboratories]

Studies in the Cyanine Dye Series. X.[1] Reactivity of the Methyl Group in Quaternary Salts of 3-Methylisoquinoline[2]

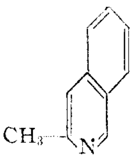
By L. G. S. Brooker and F. L. White

The 3-methyl group in 2-alkyl-3-methylisoquinolinium salts undergoes condensation with *p*-dimethylaminobenzaldehyde and certain other aldehydes in the presence of piperidine to give high yields of condensation products. Attempts to carry out a variety of other condensations leading to cyanine dyes were unsuccessful, although very low yields of symmetrical carbocyanines could be obtained using more drastic conditions than usual. The unsuccessful results may be correlated in large measure with the relative difficulty of liberating the intermediate methylene bases (VIII) by removal of the elements of acid from the quaternary salts, ascribable to the exceptionally high basicity of these methylene bases.

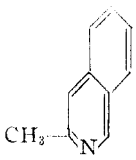
In their comparison of the isomeric 1- and 3-methylisoquinolines, which they formulated using the Erlenmeyer structures I and II, respectively, Mills and Smith[3] found the methyl group in I and its quaternary salts to be highly reactive, while that in II and its salts appeared to be totally unreactive. These negative results they correlated with the predominantly single-bond character of the linkage in II between nitrogen and carbon atom 3, conjugation between nitrogen and the methyl group, by the shortest route, being interrupted.



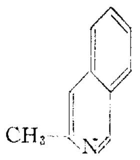
I



II



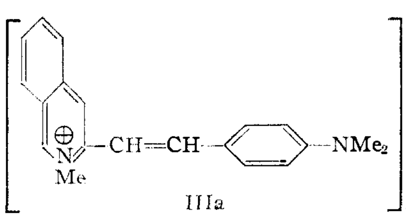
IIa



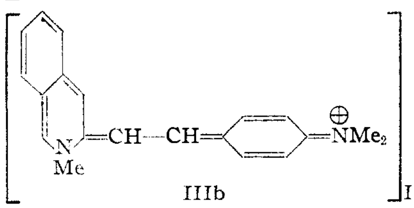
IIb

The nitrogen atom is nevertheless conjugated with the methyl group around the periphery of the pyridine ring in II and, furthermore, from a modern standpoint, the linkage between nitrogen and carbon atom 3 would be expected to have some double-bond character, since this linkage is a double bond in one of the three most probable contributing structures (II, IIa, IIb).

With these considerations in mind, we were led to a re-examination of the reactivity of the methyl group in II, which has become commercially available in recent times. Contrary to the experience of Mills and Smith, the methiodide of II was found to condense with *p*-dimethylaminobenzaldehyde in ethyl alcoholic solution, using piperidine as a catalyst, to give a yellow-orange dye (III), although the yield was only 7%. If the alcohol was omitted, however, the two components and the piperidine being fused together at about 135°, the yield was increased to 67%, and to 79% when 100% excess of the aldehyde was used. The ethiodide corresponding to III was similarly obtained, the three yields corresponding to the conditions given above being 7, 61 and 79%, respectively.[4]

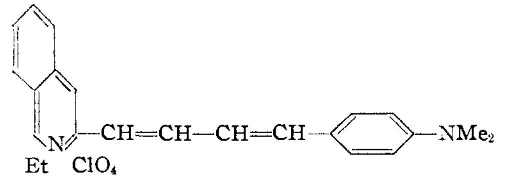


IIIa

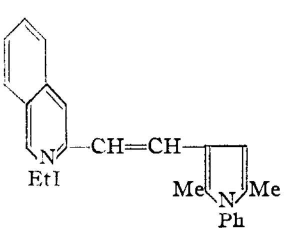


IIIb

The alkyl iodides of 3-methylisoquinoline also underwent condensation with *p*-dimethylaminocinnamaldehyde, dye IV, for example, being obtained in a yield of 34%. Other aromatic aldehydes that condensed with these salts are benzaldehyde and *m*-nitrobenzaldehyde. Perhaps the most striking result obtained with aldehydes was furnished by 2,5-dimethyl-1-phenyl-3-pyrrolecarboxaldehyde,[5] for, under the best conditions, this yielded unsymmetrical isoquinopyrrolocarbocyanines such as V in yields that were either quantitative or nearly so.



IV



V

In their condensations with aldehydes, quaternary alkyl salts of II thus showed considerable reactivity. Nevertheless they failed to undergo a number of other condensations that, if successful, would have yielded cyanine dyes. Thus, attempts to condense them with 2-iodoquinoline ethiodide or 2-methyl-(or phenyl)-thiolquinoline ethiodide in the presence of triethylamine or of potassium hydroxide were fruitless. Again, attempts to condense them with ethyl orthoformate in pyridine solution were

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(1) Part IX, see This Journal, **59**, 2697 (1937).

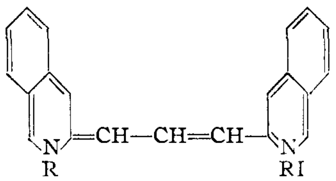
(2) Presented before the Organic Section of the American Chemical Society, April 11, 1946, at Atlantic City, New Jersey. A paper dealing with the reactivity of the 3-methyl group in 3-methylisoquinoline and its salts has, in the meantime, been published by Erlenmeyer, Baumann and Sorkin [*Helv. Chim. Acta*, **31**, 1978 (1948)].

(3) Mills and Smith, *J. Chem. Soc.*, **121**, 2724 (1922).

(4) White and Brooker, U. S. Patent 2,466,523 (1949) (applied for May 25, 1946).

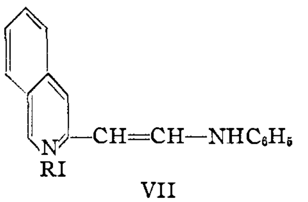
(5) Brooker and Sprague, This Journal, **67**, 1869 (1945).

unavailing, and only when the pyridine was replaced by isoquinoline as a solvent, and the reaction carried out at the refluxing temperature, could very small yields of the symmetrical carbocyanines VI be obtained.



VI

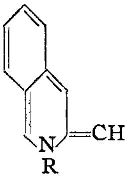
A somewhat more satisfactory method consisted in heating the 3-methylisoquinoline alkyl iodides with ethyl isoformanilide in nitrobenzene solution, but even so, the yields before recrystallization were only 6 and 4% for the dimethyl and diethyl dyes, respectively. If the salts were heated with ethyl isoformanilide alone,[6] low yields of the anilinovinyl derivatives VII were obtained.



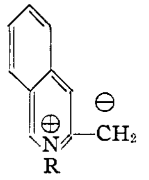
VII

From the results described above it is clear that if the reaction leading to III or V were selected to demonstrate the reactivity of the methyl group in salts of II, that reactivity would be rated as extremely high, whereas selection of one of a number of other reactions which fail to take place, would indicate lack of reactivity. This apparent inconsistency obviously requires explanation.

In the formation of the various condensation products of 3-methylisoquinolinium salts, the reactive intermediate is probably a methylene base (VIII, R = Me, Et).[3,7] In the conventional representation (VIIIa) of VIII both of the rings are *o*-quinonoidal. There is but one way of writing the structure, using only ortho linkages and omitting charged structures, and such substances would be expected to be especially unstable. In fact, in attempting to account for the non-reactivity of the methyl group in salts of II as erroneously reported by Mills and Smith,[3] Taylor and Baker pointed out that the logical intermediate VIII would have linkages analogous to those in the unknown 2,3-naphthoquinone, so that its non-existence did not seem surprising to them.[8] One would expect a relatively high contribution from the dipolar structure VIIIb which is heavily stabilized because the ring in it is fully aromatic. Nevertheless, neither of the two structures VIIIa and VIIIb possesses really high stability, and of methylene bases as a class, VIII must be especially unstable. In the reactions, however, the methylene bases need not be assumed to have more than transitory existence.

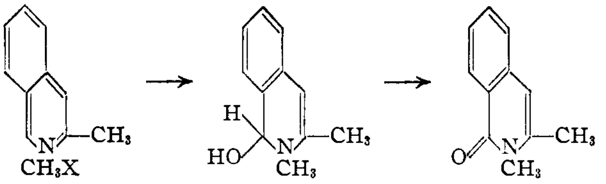


VIIIa



VIIIb

Since the quaternary salts of 3-methylisoquinoline from which the methylene bases VIII are derived (by removal of the elements of acid) are stabilized by resonance to a much greater extent than the methylene bases themselves (corresponding to the three Kekulé type structures it is possible to write for the isoquinolinium nucleus), the salts will resist the removal of acid to an exceptional degree. In other words, the methylene compounds VIII are exceedingly strong bases. This is undoubtedly the reason why only those reactions have been carried out successfully which utilize the very strong organic base piperidine as condensing agent, or else require quite drastic conditions. There seems little doubt, in fact, that the observed reactivity or otherwise of the methyl group in quaternary salts of 3-methylisoquinoline is largely a matter of whether sufficiently basic conditions are employed for the liberation of the methylene base. If such conditions are not employed, an attempted condensation will probably fail. However, quaternary salts of 3-methylisoquinoline do not yield carbocyanines with chloroform or iodoform under the influence of either sodium ethoxide or potassium hydroxide. With powerful hydroxylic bases such as these it seems likely that a competing reaction intervenes, carbinol bases, IX (stabilized by Kekulé resonance in the benzene ring), being formed in preference to a methylene base, VIII, for cold alkaline oxidation of 3-methylisoquinoline metho-*p*-toluenesulfonate gives the 2,3-dimethyl-1-isoquinolone (X).



IX X

The conditions under which salts of II undergo condensation thus appear to be narrowly defined, even though high yields of condensation products may be obtained under optimum conditions. On the one hand, sufficiently strongly basic conditions must be employed to liberate a minimum concentration of methylene base (VIII), but on the other, inorganic alkalies must be avoided.

Acknowledgments.—We take pleasure in acknowledging our indebtedness to Mr. Donald F. Ketchum and his department for the microanalyses.

Experimental

3-*p*-Dimethylaminostyryl-2-methylisoquinolinium Iodide (III).—3-Methylisoquinoline methiodide (2.85 g., 1 mol), *p*-dimethylaminobenzaldehyde (1.49 g., 1 mol), ethyl alcohol (10 ml.) and piperidine (0.3 ml.) were heated at the refluxing temperature for one hour. The yield of product

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(6) Knott, *J. Chem. Soc.*, 120 (1946).

(7) Mills and Raper, *ibid.*, **127**, 2466 (1925).

(8) Taylor and Baker in Sidgwick "Organic Chemistry of Nitrogen," 2nd edition, Oxford University Press, New York, N. Y., 1937, p. 560.

after washing with acetone and with water was 7% before and 3% after two recrystallizations from methyl alcohol. The reddish-orange crystals had m.p. 285–286° dec.

Anal. Calcd. for $C_{20}H_{21}IN_2$: I, 30.5. Found: I, 30.6.

The dye was also prepared by adding 1 ml. of piperidine to an intimate mixture of quaternary salt (1.43 g., 1 mol) and aldehyde (0.75 g., 1 mol) and heating the mixture in an oil-bath at 135–140° for 10 minutes. The yield of dye after washing was 67%, and 60% (two crops) after recrystallization. When 100% excess of the aldehyde was used, the corresponding yields were 79 and 72%.

3-*p*-Dimethylaminostyryl-2-ethylisoquinolinium iodide (*cf.* III) was prepared similarly. The minute reddish crystals had m.p. 271–272° dec.

Anal. Calcd. for $C_{21}H_{23}IN_2$: I, 29.5. Found: I, 29.5.

3-[4-(*p*-Dimethylaminophenyl)-1,3-butadienyl]-2-methylisoquinolinium perchlorate (*cf.* IV) was prepared by heating 3-methylisoquinoline methiodide (2.85 g., 1 mol), *p*-dimethylaminocinnamaldehyde (1.75 g., 1 mol), ethyl alcohol (25 ml.) and piperidine (0.3 ml.) at the refluxing temperature for one-half hour. After washing with ether, a solution of the residue in hot methyl alcohol was treated with aqueous sodium perchlorate. The yield of washed dye was 35% before and 8% after two recrystallizations from methyl alcohol. The dull reddish crystalline powder had m.p. 232–235° dec.

Anal. Calcd. for $C_{22}H_{23}ClN_2O_4$: C, 63.7; H, 5.6. Found: C, 63.4; H, 5.6.

3-[4-(*p*-Dimethylaminophenyl)-1,3-butadienyl]-2-ethylisoquinolinium perchlorate (IV) was prepared similarly. The yield of crude but washed dye (34%) was reduced to 6% after two recrystallizations. The dull reddish crystalline powder had m.p. 241–243° dec.

Anal. Calcd. for $C_{23}H_{25}ClN_2O_4$: C, 64.4; H, 5.9. Found: C, 64.2; H, 5.6.

2-Methyl-3-styrylisoquinolinium iodide was prepared by heating an intimate mixture of 3-methylisoquinoline methiodide (1.43 g., 1 mol), benzaldehyde (1.06 g., 1 mol + 100% excess) and piperidine (1 ml.) at 130–135° for 10 minutes with stirring. The yield of washed dye was 58%, and 49% after recrystallization from methyl alcohol (two crops). The cream-colored needles had m.p. 286–287° dec.

Anal. Calcd. for $C_{18}H_{16}IN$: I, 34.0. Found: I, 34.1.

2-Ethyl-3-styrylisoquinolinium perchlorate was prepared similarly, the iodide being converted to perchlorate. The yield of washed product was 45% before and 28% after recrystallization from methyl alcohol. The light brown crystals had m.p. 301–302° dec.

Anal. Calcd. for $C_{19}H_{18}ClNO_4$: C, 63.4; H, 5.0. Found: C, 63.6; H, 5.3.

2-Methyl-3-*m*-nitrostyrylisoquinolinium iodide was prepared similarly. The yield of crude but washed product was 65% before and 21% after recrystallization. The tan-colored needles had m.p. 284–286° dec.

Anal. Calcd. for $C_{18}H_{15}IN_2O_2$: I, 30.4. Found: I, 30.5.

2-Ethyl-3-*m*-nitrostyrylisoquinolinium perchlorate was obtained similarly. The 45% yield of washed dye was reduced to 27% after recrystallization. The brownish crystals had m.p. 237–238° dec.

Anal. Calcd. for $C_{19}H_{17}ClN_2O_6$: C, 56.4; H, 4.2. Found: C, 57.2; H, 4.1.

2,2′,5′-Trimethyl-1′-phenyl-3-isoquino-3′-pyrrolocarbocyanine iodide (*cf.* V).—When 3-methylisoquinoline methiodide (2.85 g., 1 mol), 2,5-dimethyl-1-phenyl-3-pyrrolecarboxaldehyde (2 g., 1 mol), piperidine (0.3 ml.) and ethyl alcohol (15 ml.) were heated together under reflux for 1 hour, a 4% yield of washed dye was obtained. Replacement of the alcohol by pyridine (40 ml.) gave an 11% yield of washed product when the period of refluxing was 35 minutes. When the solid components (but 100% excess of the aldehyde) and piperidine (2 ml.) were fused at 135–140° for 10 minutes, the yield of washed product was 86%, being 81% after recrystallization (two crops). The orange-brown crystals had m.p. 273–274° dec.

Anal. Calcd. for $C_{24}H_{23}IN_2$: I, 27.2. Found: I, 27.4.

2-Ethyl-2′,5′-dimethyl-1′-phenyl-3-isoquino-3′-pyrrolocarbocyanine Iodide (V).—When 3-methylisoquinoline ethiodide (3 g., 1 mol), 2,5-dimethyl-1-phenyl-3-pyrrolecarboxaldehyde (2 g., 1 mol), piperidine (0.3 ml.) and ethyl alcohol (15 ml.) were heated together under reflux for 1 hour, a 2% yield of washed dye was obtained. Use of pyridine (15 ml.) as solvent, and heating under reflux for 35 minutes gave a 13% yield of washed dye. Omission of solvent, doubling the proportion of aldehyde, increasing the piperidine to 2 ml. and heating to 135–140° for 10 minutes furnished a quantitative yield of washed dye, being 96% after recrystallization (two crops). The lustrous brown crystals had m.p. 269–270° dec.

Anal. Calcd. for $C_{25}H_{25}IN_2$: I, 26.4. Found: I, 26.5 (first crop); I, 26.4 (second crop).

2,2′-Dimethyl-3,3′-isoquinocarbocyanine Iodide (VI, R = CH_3).—3-Methylisoquinoline methiodide (28.5 g., 2 mols), ethyl orthoformate (22.2 g., 1 mol + 200% excess) and isoquinoline (50 ml.) were heated at the refluxing point for 45 minutes. After cooling, the residue was thoroughly washed with methyl alcohol, first cold and then hot. The average yield of crude dye from a number of runs was 1.7%.

In the alternative method the quaternary salt (5.7 g., 2 mols), ethyl isoformanilide (3 g., 1 mol + 100% excess) and nitrobenzene (15 ml.) were heated at the refluxing point for 5 minutes. After cooling, the dye was removed and washed with methyl alcohol; yield 6%.

Even after repeated recrystallization, it was difficult to obtain satisfactory analytical results on the sparingly soluble dye iodide, though the results approximated to those required. The dye was accordingly converted into the more soluble chloride.

Crude dye iodide (3.6 g.) was dissolved in cresol[9] (technical grade, 40 ml.) and treated with 100% excess of freshly precipitated silver chloride, the mixture being stirred for 4.5 hours at 100°. Dye chloride separated from the cresol filtrate on the addition of ether and was recrystallized from ethyl alcohol; yield 80%. After two further recrystallizations, the lustrous reddish-brown crystals had m.p. 304–306° dec.

Anal. Calcd. for $C_{23}H_{21}ClN_2$: Cl, 9.8. Found: Cl, 10.0.

2,2′-Diethyl-3,3′-isoquinocarbocyanine iodide (**VI**, R = C_2H_5) was prepared in a similar manner. By the ethyl orthoformate–isoquinoline procedure, the average yield of washed dye obtained in several runs was 2.2%, and 4% by the ethyl isoformanilide–nitrobenzene method. After several recrystallizations from methyl alcohol the dye was obtained in lustrous brownish-red needles with m.p. >330°.

Anal. Calcd. for $C_{25}H_{25}IN_2$: C, 62.5; H, 5.3; I, 26.4; N, 5.8. Found: C, 61.6; H, 5.3; I, 26.2; N, 6.1.

Some of the dye iodide was converted into the chloride as described above. The brown needles had m.p. 285–286° dec.

Anal. Calcd. for $C_{25}H_{25}ClN_2$: Cl, 9.1; N, 7.2. Found: Cl, 9.1; N, 7.1.

3-Anilinovinyl-2-ethylisoquinolinium iodide (**VII**, R = C_2H_5).—3-Methylisoquinoline etho-*p*-toluenesulfonate (17.1 g., 1 mol; prepared by heating the base with ethyl *p*-toluenesulfonate at 100° for 3 hours and washing the cooled, crushed product with acetone) and ethyl isoformanilide (14.9 g., 1 mol + 100% excess) were heated together at about 185° for 3 hours. The product was dissolved in hot methyl alcohol and treated with hot aqueous potassium iodide. The solid which separated was well washed; yield 14%. After recrystallization from methyl alcohol the brownish crystals had m.p. 264–265° dec.

Anal. Calcd. for $C_{19}H_{19}IN_2$: C, 56.7; H, 4.8; I, 31.6. Found: C, 56.7; H, 4.8; I, 31.7.

2,3-Dimethyl-1(2H)-isoquinolone (**X**).—3-Methylisoquinoline metho-*p*-toluenesulfonate (164.5 g., 1 mol; prepared in similar manner to the above etho-*p*-toluenesulfonate) was dissolved in water (500 ml.) at 5–10° and the solution slowly added with stirring to a chilled solution of potassium ferricyanide (362 g., 2 mols + 10% excess) and 85% potassium hydroxide (132 g., 4 mols) in water (1100 ml.), the temperature being kept between 7 and 11°. The solution was kept for a further two hours, extracted with three 1-liter portions of benzene, the combined extracts washed with water, dried with anhydrous magnesium sulfate, the benzene removed by evaporation and the residue fractionated under

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(9) Brooker, U. S. Patent 2,245,249 (1941).

reduced pressure. The fraction of b.p. 153–163° (1 mm.) (12.1 g., 14% yield) was purified by three recrystallizations from ligroin (b.p. 60–90°). The almost colorless lath-like crystals had m.p. 101–102°; yield 7%.

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.3; H, 6.4. Found: C, 76.6; H, 6.3.

Gabriel and Neumann[10] who prepared this compound by another method give m.p. 103°. It was obtained as an oil by Erlenmeyer, Baumann and Sorkin.[2]

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[10] Gabriel and Neumann, *Ber.*, **25**, 3563 (1892).

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Polyarylene-alkylene Sulfides[1]

BY C. S. MARVEL AND P. D. CAESAR[2]

Aryl dithiols and biallyl react in emulsion polymerization systems to produce polyarylene-alkylene sulfides of high molecular weight and high melting point. Some of these polymers give orientable fibers on cold drawing. The introduction into the emulsion of an inert organic solvent such as benzene or methanol and an increase in polymerization temperature improves the yields when high melting dithiols are used in these polymerizations. Methods for the preparation and purification of some aryl dithiols have been evaluated and developed.

The present work was undertaken to see if aryl dithiols would copolymerize with non-conjugate aliphatic diolefins to form linear, high molecular weight polymers similar to the polyalkylene sulfides obtained in the earlier work in this Laboratory.[3] It was found that the resultant polyarylene-alkylene sulfides were crystalline fibrous polymers of higher melting point than the polyalkylene sulfides, and an investigation of the effect of the structure of the aryl dithiol monomer on the properties of the polymer was carried out with the particular purpose of increasing the melting point as much as possible. Biallyl was used as the aliphatic diolefin throughout this work.

An emulsion polymerization technique similar to that described by Marvel and Aldrich[3b] was found to be the most satisfactory method of polymerization. However, the presence of a solid insoluble monomer presented features which were novel to such systems. When an initiator system consisting of ammonium persulfate, sodium hydrogen sulfite and cupric sulfate[4] was used at 30° with the emulsifier, MP-189-EF,[5] buffered with sodium acetate and adjusted to a *p*H of 3.35,[6] it was found that a small amount of an organic solvent, such as benzene or methanol, in the system increased the yield of higher molecular weight polyarylene-alkylene sulfides. It was necessary, of course, to use a solvent which was inert to the monomers. Although a small amount of solvent solubilized the solid monomer sufficiently to facilitate polymerization, larger amounts had a deleterious effect as shown in Tables I and II. It was found, too, that the yield and molecular weight of polyarylene-alkylene sulfides of higher melting point and lower solubility could be increased by employing a polymerization temperature of 50° and higher (see Table III). At these temperatures no reducing agent could be tolerated in the system.

The polymers from aryl dithiols with biallyl showed an increase in melting point from the maximum of 86° for polyalkylene sulfides thus far obtained[3a] to 225–235° for the polyarylene-alkylene sulfide prepared from biphenyl-4,4′-dithiol and biallyl. This effect on the melting point was more noticeable when such a polynuclear group was introduced into the polymer than when the various isomeric forms of a condensed nucleus like naphthalene were incorporated therein. The polyarylene-alkylene sulfides of high melting point had very low solubilities in organic solvents.

With the exception of melting point and solubility in organic solvents, however, the polyarylene-alkylene sulfides were similar in properties to the polyalkylene sulfides. The polymers with inherent viscosities of the order of 0.4 and higher melted sharply and yielded fibers from a melt. These fibers could be cold-drawn. X-Ray diffraction patterns showed crystallinity in the original polymer and orientation in the stretched fiber.[7] The strength of these polymers seemed to be as much a function of the type of monomeric dithiol as of the molecular weight. For example, two polymers obtained by the polymerization of diphenylmethane-4,4′-dithiol and phenoxybenzene-4,4′-dithiol with biallyl, although of similar melting point and inherent viscosity, gave very strong and weak fibers, respectively.

Two methods for the preparation of aryl dithiols were utilized. The first was the reduction of aryl sulfonyl chlorides with zinc dust and acid.[8] It was found that more reproducible results could be obtained by amalgamation of the zinc dust prior to its use as a reducing agent. This process seemed to be limited, however, to the reduction of those aryl disulfonyl chlorides that gave aryl dithiols of relatively low melting point and high solubility. For the preparation of the less soluble aryl dithiols of higher melting point it was necessary to use a second, less familiar reduction technique. In this

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[1] This is the ninth communication on polyalkylene sulfides. For the eighth see C. S. Marvel and C. W. Roberts, *J. Poly. Sci.*, in press.

[2] Recipient of Socony-Vacuum Oil Company Scholarship in Chemistry 1947–1950.

[3] (a) C. S. Marvel and R. R. Chambers, THIS JOURNAL, **70**, 993 (1948); (b) C. S. Marvel and P. H. Aldrich, *ibid.*, **72**, 1978 (1950).

[4] R. G. R. Bacon, *Trans. Faraday Soc.*, **42**, 140 (1946); L. B. Morgan, *ibid.*, **42**, 169 (1946).

[5] MP-189-EF is an electrolyte-free emulsifier which consists essentially of mixed alkanesulfonic acids. We are indebted to Dr. Stanley Detrick of Jackson Laboratory, E. I. du Pont de Nemours and Company, for this material.

[6] C. S. Marvel and G. Nowlin, THIS JOURNAL, **72**, 5026 (1950).

[7] We are indebted to Dr. J. Fuchs and Professor G. L. Clark for these X-ray studies.

[8] R. Adams and C. S. Marvel, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 504.