and streptococcus antitoxins and of anti-influenza A likewise are substantially unchanged.

It will be noted as well that the immunological assay values have not fallen off during a one year period.

Discussion and Conclusions

The best conditions for the production of half molecules of human gamma globulin appear to be digestion at *p*H 3.5 for three days with at least 0.05 P. U. Hb per gram of globulin. About 70% of the protein remains in nondialyzable form; of this material 60 to 70% is present as halves of the normal globulin.

If the pepsin ratio is reduced to 0.01 unit per gram of globulin, an equivalent amount of half molecules is formed, but about 20% of unchanged globulin remains. Also, with reduced relative amounts of pepsin, periods of more than three days are necessary for "equilibrium" to be attained at temperatures near 0°.

The advantages of digested gamma globulin antibodies lie in their smaller particle size. The viscosity of concentrated (16%) solutions is much less than that of the unsplit globulin in solution of like concentration. This makes the final product much easier to handle. The smaller molecules may also be presumed to have an increased rate of diffusion, not only through body fluids, but also across membranes.

Acknowledgment.—This work was made possible by a grant from the Rockefeller Foundation. It is also a pleasure to acknowledge the kindness of Drs. Mary L. Petermann and J. W. Williams whose helpful discussions have been of great aid in its performance.

Summary

1. Human gamma globulin is split by pepsin into molecules of half size. Further digestion leads to the formation of smaller particles and ultimately to dialyzable fragments.
2. The yield of half-molecules is greatest when digestion is carried out at *p*H 3.5 for three days, in the cold, with at least 0.05 hemoglobin unit of pepsin per gram of globulin.
3. Attempts to separate the half molecules from both unsplit globulin and smaller fragments by fractionation with ammonium sulfate or ethanol were partially successful.

WORCESTER, MASS. RECEIVED DECEMBER 1, 1945

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

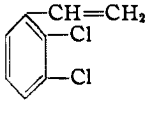
The Preparation and Polymerization of the Six Nuclear Isomeric Dichlorostyrenes[1,2]

BY C. S. MARVEL, C. G. OVERBERGER, R. E. ALLEN, H. W. JOHNSTON, J. H. SAUNDERS AND J. D. YOUNG

Introduction

The recent article of Michalek and Clark[3] reporting the boiling points, refractive indices and densities of the six-nuclear substituted dichlorostyrenes and the properties of one unidentified polydichlorostyrene has prompted us to present here some experiments which have been carried out on these products in our laboratory. Except for the above report, nothing has been found in the literature concerning the 2,3- (I), 2,4- (II), 2,6- (IV) and 3,5- (VI) dichlorostyrenes.

Brooks[4] has reported the synthesis of the 2,5 isomer (III) from 2,5-dichlorobenzaldehyde and the 3,4 isomer (V) from 3,4-dichloroacetophenone. Michalek and Clark[3] state that the 2,5 and 3,4 isomers have been made from the corresponding dichlorobenzaldehyde without giving experimental details. The 2,5 isomer (III) used in our experiments was obtained as a gift from the Monsanto Chemical Company. We have made all of the other isomeric dichlorostyrenes from the corresponding aldehydes by the Grignard reaction followed by dehydration of the methyl carbinol. These processes are described below. In addition other methods of synthesis are described for certain of the monomers and a brief description and characterization of the polymers of these isomeric dichlorostyrenes is included in this paper.



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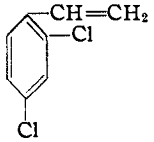

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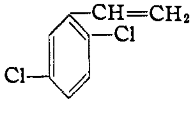

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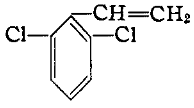

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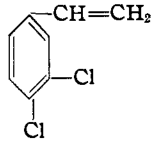

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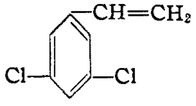

VI

Experimental

2,3-Dichlorotoluene

Our synthesis of this monomer is outlined below.

We used the method of Hadfield and Kenner[5] to convert *o*-toluidine to 3-nitro-2-aminotoluene. Cohen and

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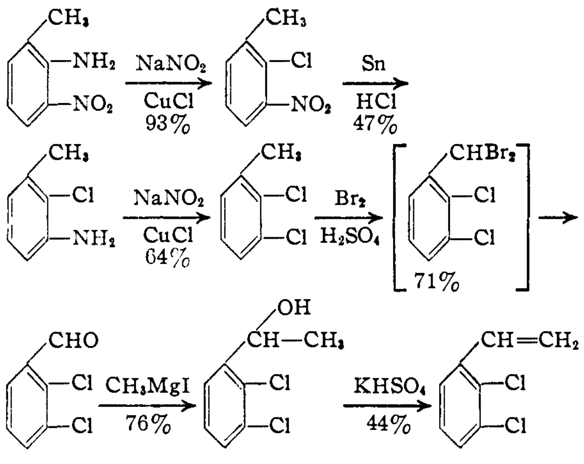
[1] Most of the work described in this manuscript was done under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Government Synthetic Rubber Program.

[2] This is the twenty-first communication on vinyl polymers. For the twentieth see THIS JOURNAL, **68**, 736 (1946).

[3] Michalek and Clark, *Ind. Eng. Chem., News Ed.*, **22**, 1559 (1944).

[4] Brooks, THIS JOURNAL, **66**, 1295 (1944).

[5] Hadfield and Kenner, *Proc. Chem. Soc.*, **30**, 253 (1914).



Dakin[6] have converted 3-nitro-2-aminotoluene to 3-nitro-2-chlorotoluene but do not give much detail in their article. We followed essentially the method described in "Organic Syntheses"[7] for the preparation of *m*-nitrochlorobenzene in our work. The reduction of the nitro compound was by tin according to usual methods. Since Cohen and Dakin[6] did not characterize 2,3-dichlorotoluene in detail, we have analyzed our material.

2,3-Dichlorotoluene.—The experimental details of this procedure are those described for the preparation of *m*-nitrochlorobenzene. From 90 g. of 3-amino-2-chlorotoluene there was obtained 65 g. (64%) of 2,3-dichlorotoluene, b. p. 61–62° (3 mm.); n^{20}_D 1.5511.

Anal.[8] Calcd. for $C_7H_6Cl_2$: C, 52.20; H, 3.75. Found: C, 52.31; H, 3.70.

2,3-Dichlorobenzaldehyde.—The procedure employed was similar to that described by Lock and Bock[9] for the preparation of 2,4-dichlorobenzaldehyde. From 55 g. of 2,3-dichlorotoluene there was obtained 42 g. (71%) of 2,3-dichlorobenzaldehyde, m. p. 58–60°. A small sample was recrystallized for analysis from a 50-50 water–ethanol mixture, m. p. 65–67°.

Anal. Calcd. for $C_7H_4OCl_2$: C, 48.03; H, 2.30. Found: C, 47.81; H, 2.43.

2,3-Dichlorophenylmethylcarbinol.—The procedure employed was similar to that described by Lock and Bock[9] for the preparation of 2,4-dichlorophenylmethylcarbinol. From 40 g. of 2,3-dichlorobenzaldehyde there was obtained 33 g. (76%) of 2,3-dichlorophenylmethylcarbinol, b. p. 112–113° (2 mm.), m. p. 55–57°.

Anal. Calcd. for $C_8H_8OCl_2$: C, 50.28; H, 4.21. Found: C, 50.33; H, 4.28.

A 3,5-dinitrobenzoate was prepared in the usual manner.[10] The solid dinitrobenzoate was only slightly soluble in 95% ethanol; however, this solvent was highly satisfactory for recrystallization if enough solvent was employed, m. p. 145–146°.

Anal. Calcd. for $C_{15}H_{10}N_2O_6Cl_2$: N, 7.27. Found: N, 7.09.

2,3-Dichlorostyrene.—In a 125-cc. Claisen flask were placed 20 g. of fused potassium acid sulfate, 2 g. of hydroquinone and 1 g. of *p*-*t*-butylcatechol. The flask was filled with a dropping funnel and a distilling flask was attached to the side arm. The flask and its contents were heated to 220–230° by means of a metal bath and the pressure reduced to 80 mm. Fifty-four grams of carbinol was dropped slowly onto the potassium acid sulfate over a period of one hour. The mixture of water, styrene and carbinol which distilled was collected and the water separated. The organic layer was dissolved in 400 cc. of ether and the ether solution was washed with 5% sodium hydroxide solution, then twice with water and dried over anhydrous magnesium sulfate. The drying agent and solvent were removed and the residue distilled through a six-inch, helices-packed column. The following fractions were collected.

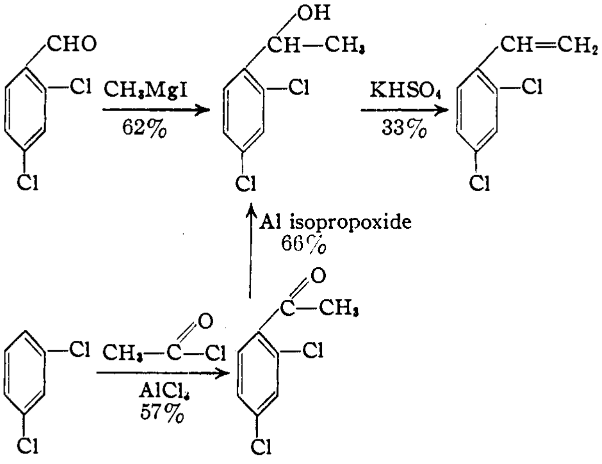
Fraction no.	Wt., g.	B. p., °C.	Mm.	n^{20}_D	d^{20}_{20}
1	2	92	4-5		
2	19	92-94	4-5	1.5848	1.2849
				n^{25}_D 1.5809	
3	6	94-130	4-5		

A small residue polymerized. The yield was 19 g. (fraction 2) or 44% of the theoretical amount taking into account the recovered carbinol (fraction 3). Michalek and Clark[3] reported a boiling point of 61° (1 mm.), n^{25}_D 1.5780, d^{25}_4 1.264.

Anal. Calcd. for $C_8H_6Cl_2$: C, 55.52; H, 3.49. Found: C, 55.64; H, 3.54.

2,4-Dichlorostyrene

The two following synthetic routes were employed to prepare 2,4-dichlorophenylmethylcarbinol which was dehydrated to the styrene.



II

2,4-Dichlorotoluene prepared by the method of Hodgson and Walker[11] was converted successively to 2,4-dichlorobenzaldehyde and 2,4-dichlorophenylmethylcarbinol by the procedure described by Lock and Bock.[9] This carbinol was also prepared from *m*-dichlorobenzene by acetylation and reduction.

2,4-Dichloroacetophenone from *m*-Dichlorobenzene.—The method was adapted from that of Roberts and Turner[12] for 3,4-dichloroacetophenone from *o*-dichlorobenzene. From 40 g. of *m*-dichlorobenzene there was obtained 29 g. (57%) of 2,4-dichloroacetophenone, b. p. 123° (12 mm.), n^{20}_D 1.5642.

Reduction of 2,4-Dichloroacetophenone.—The ketone was reduced to the corresponding 2,4-dichlorophenylmethylcarbinol by aluminum isopropoxide in isopropyl alcohol by a standard procedure.[13] From 49 g. of 2,4-dichloroacetophenone and 106 g. of aluminum isopropoxide there

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(6) Cohen and Dakin, *J. Chem. Soc.*, **79**, 1128 (1901).

(7) Hartman and Brethen, "Organic Syntheses," 2nd ed., Coll. Vol. I, John Wiley and Sons, Inc., New York, 1941, p. 162.

(8) All analyses reported in this manuscript are microanalyses by Mr. H. S. Clark of the Illinois State Geological Survey.

(9) Lock and Bock, *Ber.*, **70**, I, 923 (1937).

(10) Shriner and Fuson, "The Systematic Identification of Organic Compounds," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1940, p. 138.

(11) Hodgson and Walker, *J. Chem. Soc.*, 530 (1935).

(12) Roberts and Turner, *ibid.*, 1855 (1927).

(13) Wilds, *Reduction with Aluminum Alkoxides*, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 178.

was obtained 33 g. (67%) of 2,4-dichlorophenylmethylcarbinol, b. p. 127° (7 mm.).

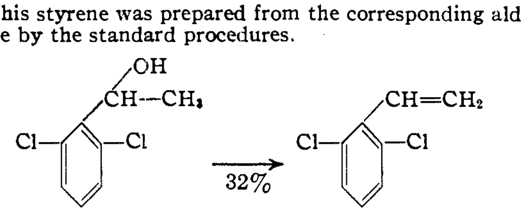
In order to confirm the position of the nuclear chlorine atoms, oxidation was carried out according to the directions described by Shriner and Fuson.[14] The solid was obtained as a white powder after two recrystallizations from dilute alcohol, m. p. 157–158°. A mixed melting point with a known sample of 2,4-dichlorobenzoic acid did not lower the melting point. Cohen and Dakin[6] have reported a melting point of 159–160° for 2,4-dichlorobenzoic acid.

2,4-Dichlorostyrene.—The general method of Brooks[4] for related compounds was adopted to this preparation. From 233 g. of 2,4-dichlorophenylmethylcarbinol there was obtained 55 g. of 2,4-dichlorostyrene, b. p. 81° (6 mm.), $n^{20}\mathrm{D}$ 1.5828, d^{25}_{4} 1.243. Forty-nine grams of carbinol was recovered. The yield based on recovered carbinol was 33%.

Anal. Calcd. for $C_8H_6Cl_2$: C, 55.52; H, 3.49. Found: C, 55.59; H, 3.48.

2,6-Dichlorostyrene

This styrene was prepared from the corresponding aldehyde by the standard procedures.



IV

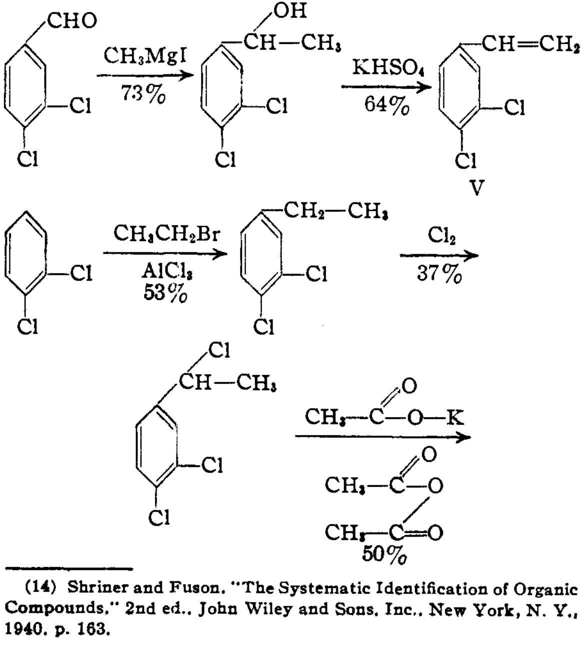
The procedure of Lock and Bock[9] for the synthesis of 2,6-dichlorophenylmethylcarbinol was used.

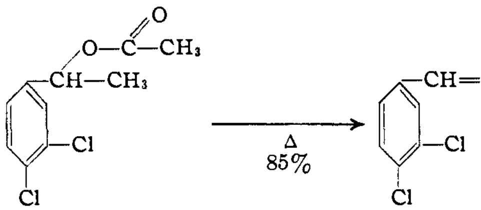
2,6-Dichlorostyrene.—The method was similar to that described for the preparation of 2,3-dichlorostyrene. From 483 g. of 2,6-dichlorophenylmethylcarbinol, there was obtained 138 g. (31.5%) of 2,6-dichlorostyrene, b. p. 64–65° (3 mm.), $n^{20}\mathrm{D}$ 1.5752, $n^{25}\mathrm{D}$ 1.5727, d^{20}_{4} 1.2641. Michalek and Clark[3] gave the following constants for 2,6-dichlorostyrene, b. p. 59° (2 mm.), $n^{25}\mathrm{D}$ 1.5724, d^{25}_{4} 1.280.

Anal. Calcd. for $C_8H_6Cl_2$: C, 55.52; H, 3.49; Cl, 40.98. Found: C, 55.11; H, 3.53; Cl, 41.39.

3,4-Dichlorostyrene

3,4-Dichlorostyrene has been synthesized from the corresponding aldehyde and it has also been prepared from *o*-dichlorobenzene. The following outline indicates these preparations.





V

3,4-Dichlorophenylmethylcarbinol.—The procedure was adapted from that of Lock and Bock[9] who prepared similar compounds by this method. From 525 g. of 3,4-dichlorobenzaldehyde, there was obtained 420 g. (73%) of 3,4-dichlorophenylmethylcarbinol, b. p. 125–130° (3–4 mm.), $n^{20}\mathrm{D}$ 1.5632. Brooks[4] has reported $n^{20}\mathrm{D}$ 1.5628 for 3,4-dichlorophenylmethylcarbinol prepared from 3,4-dichloroacetophenone.

3,4-Dichloroethylbenzene.—In a 3-liter, three-necked, round-bottomed flask was placed 2000 g. (13.6 moles) technical *o*-dichlorobenzene, and 185 g. of anhydrous aluminum chloride. The flask was equipped with a mechanical stirrer, dropping funnel and reflux condenser with gas trap attached. During the course of two hours, 1300 g. (11.9 moles) of ethyl bromide was added to the reaction flask.

After the addition was completed, stirring was continued for twenty-four hours without heating. At the end of this time the reaction mixture was poured into 1500 cc. of iced dilute hydrochloric acid. The organic layer was separated, washed with water, and dried over 25 g. of anhydrous sodium sulfate. The drying agent was removed and the residue distilled through a six-inch helices-packed column at reduced pressure. The recovered *o*-dichlorobenzene boiled at 45–65° (3 mm.). The yield was 630 g. or 31.5%. The 3,4-dichloroethylbenzene boiled at 65° (3 mm.), $n^{20}\mathrm{D}$ 1.5411, d^{25}_{25} 1.20. The yield was 1256 g. or 52.8% of the theoretical amount.

Anal. Calcd. for $C_8H_8Cl_2$: C, 54.86; H, 4.61. Found: C, 54.58; H, 4.42.

In order to confirm the position of the ethyl group, the 3,4-dichloroethylbenzene was oxidized by a conventional procedure.[13] Recrystallization of the reaction product from an aqueous ethanol solution gave a white solid melting at 201–202°. Cohen and Dakin[6] reported a melting point of 200–201° for 3,4-dichlorobenzoic acid.

3,4-Dichloro-α-chloroethylbenzene.—In a 3-liter, three-necked, round-bottomed flask was placed 1716 g. (9.8 moles) of 3,4-dichloroethylbenzene. The flask was suspended directly over a 60-watt bulb and a reflux condenser with gas trap, a sealed stirrer, and a chlorine bubbler were attached. All joints were of glass.

Chlorine was bubbled into the reaction mixture until the flask and its contents showed a gain in weight of 178 g. (5.0 atoms of chlorine). The reaction required forty-eight hours.

The reaction mixture was washed with sodium carbonate solution and water. The product was dried over 50 g. of anhydrous sodium sulfate, the drying agent removed and the product was distilled through a six-inch helices-packed column at reduced pressure. The yield of recovered 3,4-dichloroethylbenzene was 891 g. or 52% of the theoretical amount. The 3,4-dichloro-α-chloroethylbenzene boiled at 83–85° (4 mm.), $n^{20}\mathrm{D}$ 1.5631, d^{25}_{25} 1.36. The yield was 754 g. or 36.8% of the theoretical amount.

Anal. Calcd. for $C_8H_7Cl_3$: C, 45.84; H, 3.37. Found: C, 45.85; H, 3.28.

In order to confirm the structure, oxidation was carried out by a procedure similar to that employed in the oxidation of 3,4-dichloroethylbenzene. The acid melted at 198–200° thus confirming that it was the 3,4-dichlorobenzoic acid.

α-Methyl-3,4-dichlorobenzyl Acetate from 3,4-Dichloro-α-chloroethylbenzene.—In a 1-liter, three-necked, round-bottomed flask equipped with a stirrer, stopper and reflux condenser were placed 50 g. (0.24 mole) 3,4-dichloro-α-

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[14] Shriner and Fuson, "The Systematic Identification of Organic Compounds," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1940, p. 163.

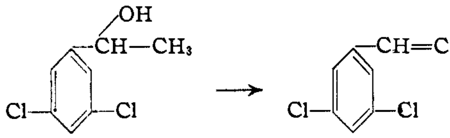
chloroethylbenzene, 44 g. (0.5 mole) potassium acetate and 250 cc. of acetic anhydride. The contents of the flask was stirred and heated for fifteen hours. The reaction mixture was then shaken with 600 cc. of water and the oil quickly separated. The aqueous layer was extracted with 50 cc. of carbon tetrachloride, the oil and extract were combined and dried over 5 g. anhydrous sodium sulfate. The solvent and drying agent were removed and the residue distilled through a six-inch helices-packed column at reduced pressures. A forerun of 3,4-dichloro-α-chloroethylbenzene boiled at 83–85° (4 mm.). The yield was 18 g. or 36%. The acetate boiled at 100–102° (4 mm.), n^{20}_{D} 1.5268, d^{25}_{25} 1.26. The yield was 27.5 g. or 49.6% of the theoretical amount.

Anal. Calcd. for $C_{10}H_{10}O_2Cl_2$: C, 51.50; H, 4.33. Found: C, 51.94; H, 4.19.

3,4-Dichlorostyrene. (A) **From Dehydration of 3,4-Dichlorophenylmethylcarbinol.**—The procedure was similar to that described for the preparation of 2,3-dichlorostyrene. From 200 g. of 3,4-dichlorophenylmethylcarbinol there was obtained 115 g. (63.7%) of 3,4-dichlorostyrene, b. p. 95° (5 mm.), n^{20}_{D} 1.5851. Brooks[4] reported a boiling point of 84° (4 mm.), n^{20}_{D} 1.5857.

(B) **From Pyrolysis of the Acetate.**—Into a vertical, 20-mm. Pyrex tube packed with twelve inches of glass beads and maintained at 550–575° was dropped 155 g. α-methyl-3,4-dichlorobenzylacetate at the rate of one drop per second. The product was distilled through a six-inch helices-packed column at reduced pressure. The pure 3,4-dichlorostyrene boiled at 88–89° (5 mm.), n^{20}_{D} 1.5844. The yield was 97.6 g. or 84.8% of the theoretical amount. No acetate was recovered.

3,5-Dichlorostyrene



VI

3,5-Dichlorotoluene was prepared by the method of Asinger and Lock[15] and also by a modification of their procedure. This modification for converting 3,5-dichloro-2-acetaminotoluene into 3,5-dichlorotoluene eliminated the time-consuming steam distillation of the 3,5-dichloro-2-aminotoluene, as described by Asinger and Lock.[15] The 3,5-dichlorotoluene was converted to the 3,5-dichlorobenzaldehyde by the method of Lock and Bock.[9]

The Direct Conversion of 3,5-Dichloro-2-acetaminotoluene to 3,5-Dichlorotoluene.—Into a 2-liter, roundbottomed flask, equipped with a reflux condenser, were placed 100 g. (0.46 mole) of 3,5-dichloro-2-acetamino-toluene, 500 cc. of 95% ethanol and 300 cc. of concentrated hydrochloric acid. This mixture was then allowed to reflux for ten hours. The hydrolysis mixture was cooled to 0° in an ice–salt mixture with efficient stirring and 32 g. (0.46 mole) of solid sodium nitrite was added slowly, keeping the temperature below 5°. When all the sodium nitrite had been added, the mixture was allowed to come to room temperature with stirring and finally heated at 60° until the evolution of nitrogen had ceased. The reaction mixture was then submitted to steam distillation. The alcohol which distilled first was diluted with water to precipitate any 3,5-dichlorotoluene which had distilled with the alcohol. The 3,5-dichlorotoluene was dissolved in ether and the solution was dried overnight over anhydrous magnesium sulfate. The solvent was removed and the residue was distilled through a six-inch all-glass, helices-packed column. The product boiled at 78–79° (9 mm.) (m. p. 24.5°), n^{20}_{D} 1.5438. The yield was 25 g. or 34% of the theoretical amount. Asinger and Lock[15] reported a melting point of 26° for 3,5-dichlorotoluene.

3,5-Dichlorophenylmethylcarbinol.—The procedure was adapted from that of Lock and Bock.[9] From 47.5 g. of 3,5-dichlorobenzaldehyde there was obtained 39 g. (69%) of 3,5-dichlorophenylmethylcarbinol, b. p. 126° (4 mm.), n^{20}_{D} 1.5573. Lock and Bock[9] characterized this carbinol by oxidation to the 3,5-dichloroacetophenone with subsequent formation of the oxime.

Anal. Calcd. for $C_8H_8OCl_2$: C, 50.29; H, 4.22. Found: C, 50.14; H, 4.44.

3,5-Dichlorostyrene.—The procedure used was similar to that described for the preparation of 2,3-dichlorostyrene. From 142 g. of 3,5-dichlorophenylmethylcarbinol, there was obtained 56 g. (43%) of 3,5-dichlorostyrene, b. p. 59° (1 mm.), n^{25}_{D} 1.5745, d^{25}_{4} 1.225. Michalek and Clark[3] reported a boiling point of 53.5° (1 mm.), n^{25}_{D} 1.5745, d^{25}_{4} 1.237.

Anal. Calcd. for $C_8H_6Cl_2$: C, 55.52; H, 3.49. Found: C, 55.83; H, 3.50.

A dibromide was prepared by the addition of bromine in glacial acetic acid to 2 g. of 3,5-dichlorostyrene until the color of bromine persisted in the solution. The solution was boiled for several minutes to drive off excess bromine, and then cooled and diluted with water. The solid dibromide was collected on a filter, washed with water and recrystallized from dilute ethanol; m. p. 89.5–90°.

Anal. Calcd. for $C_8H_6Cl_2Br_2$: C, 28.85; H, 1.81. Found: C, 28.93; H, 1.81.

Preparation of Polymers.—In a Pyrex test-tube was placed 1 g. of a dichlorostyrene. The test-tube was suspended under an ultraviolet lamp and left there until a hard polymer had been formed (about twenty-four hours). The polymer was dissolved in 50 cc. of benzene or chloroform and precipitated by slowly dropping the solution into 300 cc. of methanol with vigorous mechanical stirring. This process of purification was repeated and the powder obtained was dried for one week in a vacuum desiccator. An approximate molecular weight was determined by viscosity measurement on a benzene solution with the use of an equation developed by Kemp and Peters[16] for the determination of the molecular weight of polystyrene using the *k* value for styrene. The analyses and physical properties of these six polymers are described in Table I.

TABLE I

PROPERTIES OF DICHLOROSTYRENE POLYMERS

Polymer of dichloro-styrene isomer	Approx. mol. wt.	Softening point, °C.	Analyses,[a] % Found C	H	Cl
2,3-	17,950	195–215	55.52	3.87	40.57
2,4-	11,530	190–205	55.83	3.81	40.52
2,5-[b]	41,440	205–220	55.68	3.74	40.73
2,6-	10,890	205–238	55.49	3.57	39.68
3,4-	17,500[c]	220–235	55.65	3.54	40.49
3,5-	13,900	200–220	55.61	3.84	...

[a] The empirical formula for all polymers is $(C_8H_6Cl_2)_x$ and the calculated analysis is C, 55.50; H, 3.49, and Cl, 40.99. [b] This monomer was a gift from the Monsanto Chemical Company; b. p. 84–85° at 4–5 mm.; n^{20}_{D} 1.5801; d^{20}_{20} 1.2551. [c] All these polymers were soluble in benzene except the one from 3,4-dichlorostyrene. This one was soluble in chloroform and the molecular weight was determined in such a solution.

Summary

1. The synthesis and polymerization of the nuclear isomeric dichlorostyrenes are described.

2. The polymers of these dichlorostyrenes are briefly characterized.

URBANA, ILLINOIS

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(15) Asinger and Lock, *Monatsh.*, **62**, 344 (1933).

(16) Kemp and Peters, *Ind. Eng. Chem.*, **34**, 1097 (1942).