the determination of 1,4-butanediol to approximately 2% for 1,4-cyclohexanedimethanol. For the determination of different concentrations of isophthalic acid, the standard deviation varies from 0.7 to 2.4%.

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Isomer Distribution and Identification for the Chlorination Reaction of Acetylated 3-, 4-, 5-, and 6-Chloro-2-methylanilines by Gas–Liquid Chromatography

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Isomer distributions were determined for the chlorination reaction of 3-, 4-, 5-, and 6-chloro-2-methylanilines and their identifications were made by hydrolyzing the acetylated compounds to the free amines and comparing the retention times of their isomers on three different chromatographic columns. Only 4-chloro-2-methylaniline produced all possible (three) dichloro isomers. The 3-chloro-, 4-chloro-, and 5-chloro-methylanilines produced two dichloro isomers each. One dichloro isomer, 3,5-dichloro-2-methylaniline was not produced by either of its possible precursors. Dipole moment calculations for the dichloro isomers agreed favorably with their retention times on the nonpolar substrate, Apiezon J.

During the course of experimental work in this laboratory on the reaction of phosphorus pentachloride with *o*-nitrosotoluene (*1*), the problem of identifying dichlorinated isomers of 2-methylaniline needed to be solved. An examination of the literature revealed that only a few of these compounds had been identified and reported. Consequently, a synthesis of these isomers (there are a total of six isomers) was begun by an established procedure using potassium chlorate (*2*) and the commercially available 3-chloro-, 4-chloro-, 5-chloro-, and 6-chloro-2-methylanilines. As was soon discovered, these dichlorinated derivatives were exceedingly difficult to purify and identify for two reasons: isomer contamination and/or low melting points.

This problem is presented to provide retention time standards for the identification of five of these six dichloro-2-methylaniline isomers. This was solved by synthesizing mixtures of isomers which, because of the unique nature of the synthesis, may be used to identify all the dichloro isomers solely by their retention times without isolation of the pure components. The success of this approach is corroborated by isolating two of the isomers and spectroscopically confirming their isomeric identity, and by correlation of retention times to calculated dipole moments.

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There have been numerous studies reported in the literature where isomer identification and distribution have been accomplished by gas chromatographic techniques. However, in the majority of these studies, product identification was made possible by comparing their retention times with known compounds, i.e., the analysis of isomeric diaminotoluenes with the *N*-trifluoroacetyl derivatives (*3*), the separation of mono and dichloroaniline isomers (*4*), the identification of isomeric toluidines (*5*) and the separation and identification of seven chlorinated derivatives of toluene (*6*).

Classes of organic compounds can be identified by reaction chromatography where known compounds are not required. One of the earliest studies of this type was made by Rowan (*7*) where aromatics and olefins were absorbed in sulfuric acid and catalytically hydrogenated with hydrogen. The normal paraffins were separated by molecular sieves, the olefins were removed by mercuric perchlorate, and the C_6 naphthenes were converted to aromatics by a dehydrogenation column. Consequently, with a proper selection of columns, he could assign certain peaks to a particular class of compounds. Unfortunately, the dichlorinated isomers of 2-methylaniline could not be analyzed by any of these methods.

Nevertheless, one can resort to chemical reactions which could convert each of these isomers to known chemical isomers, e.g., deamination and/or diazonium reaction displacements of the amino group by a chloro group could be successfully done. This is unnecessary, however, in the context of this study which identified unknown peaks by the comparison of their isomer retention times on three different columns which proved remarkably successful. Only two gas chromatographic columns would be required to identify all six dichloro isomers if they yielded a separate peak for each isomer. Three columns were used in this study to be assured that the 3,5-dichloro-2-methylaniline is absent and not coeluting with another isomer.

This idea of comparing isomers is similar to the Körner method of absolute orientation (*8*). Wilhelm Körner had compared the number of isomers generated from the isomeric dibromobenzenes to identify the three unknown dibromobenzenes. In this study we were starting with known isomeric

Table I. Retention Times[a] vs. Isomer Distribution

Isomer	Reaction scheme occurance	Retention times (min) for three columns			
		R_x A	R_x B	R_x C	R_x D
I. (3,4-dichloro-2-methylaniline)	A and B	4.20[b]	4.25		
		25.2[c]	25.0		
		7.45[d]	7.20		
II. (3,5-dichloro-2-methylaniline)	A and C	None		None	
III. (3,6-dichloro-2-methylaniline)	A and D	2.95			2.95
		13.4			13.6
		5.35			5.98
IV. (4,5-dichloro-2-methylaniline)	B and C		4.45	4.48	
			26.2	26.0	
			7.95	...	
V. (4,6-dichloro-2-methylaniline)	B and D		3.05		None
			13.7		
			5.85		
VI. (5,6-dichloro-2-methylaniline)	C and D			3.30	3.42
				15.0	15.1
				5.75	6.37

[a] 1-μL injections with attenuation adjusted to keep the peaks on scale. [b] Apiezon J, program temp. 175–225 °C at 6°/min. [c] Carbowax 1540, program temp. 120–220 °C at 8°/min. [d] SE-30, program temp. 100 °C (1-min hold) to 150 °C at 6°/min.

compounds and generating unknown isomers. Their identification was made, not by the number of isomers generated, but by a comparison of the identical isomers produced.

EXPERIMENTAL

Acetylation Reactions. The 3-chloro-2-methylaniline (K & K laboratories), 4-chloro-2-methylaniline (Aldrich Chemical Co.) and 5-chloro-2-methylaniline (Aldrich Chemical Co.) were acetylated by a standard procedure with acetic anhydride (*9*). The 6-chloro-2-methylaniline (Aldrich Chemical Co.) could not be acetylated by this procedure; consequently, it was acetylated with acetyl chloride. All acetylated amines were recrystallized from EtOH and H_2O, and identification was made with infrared spectroscopy by checking the nitrogen–hydrogen stretch along with their carbonyl stretch: IR (KBr) 3240, 3260, 3265, and 3282 cm^{-1} (N–H), and 1656, 1650, 1657, and 1657 cm^{-1} (C=O), respectively, for 6-chloro-, 3-chloro-, 4-chloro-, and 5-chloro-2-methylanilides.

$KClO_3$ Chlorination Reactions. The monochloro-2-methylacetanilide 3.00 g (16.4 mmol) was added to a solution of 8.4 mL of glacial HOAc and 7.2 mL concd HCl. To this chilled solution was added 0.66 g (5.38 mmol) of $KClO_3$ (Baker Reagent Grade) dissolved in 2.5 mL of hot H_2O. The solution was stoppered and stirred magnetically at room temperature overnight. Excess H_2O was added to precipitate the chlorinated products. The weights and percent yields (based on the dichloro product) were 3.06 g (86.0%), 2.48 g (69.7%), 2.63 g (63.9%), and 2.65 g (74.5%), respectively, from the 6-chloro-, 3-chloro-, 4-chloro-, and 5-chloro-2-methylacetanilides.

Hydrolysis of Dichloro-2-methylacetanilides. Each of the quantities (see above) of the dichloro-2-methylacetanilides were hydrolyzed overnight in a refluxing solution of 18 mL absolute EtOH and 14 mL concentrated HCl. After hydrolysis, 15 mL of H_2O was added, and the solutions were cooled in an ice bath. They were neutralized with 50% KOH and extracted with three 40-mL portions of diethyl ether. The ether extracts were dried over anhydrous K_2CO_3 and concentrated between 5 and 10 mL by rotary evaporation for GC analysis.

4,6-Dichloro-2-methylaniline. The 4,6-dichloro-2-methylaniline was prepared in a three-step synthesis as described above starting with 5 g (25 mmol) of 4-chloro-2-methylacetanilide. The 4,6-dichloro-2-methylacetanilide, after recrystallizing with charcoal from a solution of EtOH and H_2O, melts at 183-185 °C. Lit. 186 °C (*10*). The 4,6-dichloro-2-methylaniline was prepared from the purified 4,6-dichloro-2-methylacetanilide. The aniline derivative was recrystallized two times from EtOH and H_2O with charcoal, mp 38–39 °C. Lit. 58–60 °C (*11*). Since the mp disagreed with the literature mp, a crude sample of the amine was sublimed into fluffy white crystals, mp 42–44 °C, IR (KBr) 3490, 3395, 1615, 1470, 864, and 735 cm^{-1}; NMR ($CDCl_3$) 2.28 (s, 3 H, $-CH_3$), 3.70 (broad, 2 H, $-NH_2$), 6.93 (s, 1 H, ring hydrogen) and 7.30 (s, 1 H, ring hydrogen). The IR and NMR data plus the acetanilide derivative mp for the 4,6-dichloro-2-methylaniline was convincing proof that the compound was the correct structure regardless of the discrepancy in mp with the literature. As a further check on its purity, a gas chromatographic analysis revealed the sublimed sample contained less that 0.5% impurity.

4,5-Dichloro-2-methylaniline. The 4,5-dichloro-2-methylaniline was prepared as described above for the 4,6-dichloro isomer from 3 g of 5-chloro-2-methylacetanilide. After crystallizing from EtOH and H_2O with charcoal, the mp was 104–106 °C. Lit. 100–101 °C (*12*). The 4,5-dichloro-2-methylacetanilide was purified by recrystallizing first from EtOH and H_2O with charcoal and second from CH_3CN, mp 184–186 °C; IR (KBr) 3365, 1602, 1580, 1515, 1435, 880, and 690; NMR ($CDCl_3$) 2.15 (s, 6 H, $-Ar-CH_3$ and $N-CH_3$), 7.3 (s, 1 H, ring hydrogen) and 7.90 (s, 1 H, ring hydrogen).

Apparatus. A Perkin-Elmer Model 900 Gas Chromatograph was used in conjunction with a Perkin-Elmer Model 165 Recorder. The recorder speed was 20 mm/min with a gas flow rate of 60 mL/min as measured by a soap-film flow meter. A Carbowax 1540 (10%), KOH (3%), 6-ft, $^1/_8$-in. o.d. stainless steel column was manufactured by Perkin-Elmer Corp. The two 6-ft, $^1/_8$-in. o.d. copper columns of Apiezon J (4.8%), KOH (3.6%), and SE-30 (3.1%) were constructed in the laboratory. The Apiezon J solid support was Chromosorb P (AW) (60/80 mesh) from Varian Aerograph. The solid support for the SE-30 column was Johns-Manville Chromosorb G (AW) (60/80 mesh) which was DMCS treated. Substrates were obtained from Varian Aerograph.

Infrared spectra were recorded on a Perkin-Elmer Grating Infrared Spectrophotometer, Model 257, and the NMR spectra on a Hitachi R-20 spectrometer.

RESULTS AND DISCUSSION

If one postulates four reaction schemes, A, B, C, and D yielding the six dichloro products I–VI as depicted in Figure 1, the following observations can be made with the retention time data as shown in Table I. There are a total of six isomers produced, and one isomer always appears in two, and only two, of the four reaction schemes. Consequently, by a comparison of retention times, positive identification of these isomers was possible.

An examination of the literature reveals that melting points are reported for four of the six dichloro-2-methylanilines; 3,4-dichloro-2-methylaniline, mp 32–33 °C (*13*); 5,6-dichloro-2-methylaniline, mp 33 °C (*11*); 4,6-dichloro-2-methylaniline, mp 58–60 °C (*10*), and 4,5-dichloro-2-methylaniline, mp 100–101 °C (*12*). To our knowledge, the 3,6-dichloro-2-methyl- and 3,5-dichloro-2-methylanilines have

Table II. Retention Times (min)[a] for Dichloro- and Trichloro-2-methylanilines[b]

Compd. No.	Compound	Reactions	Retention times for 6-ft gas chromatographic columns: Carbowax 1540	SE-30
I	3,4-Dichloro-2-methylaniline	R_x A	not detectable[c]	not detectable[c]
		R_x B	17.58 ± 0.02	2.73 ± 0.00
II	3,5-Dichloro-2-methylaniline	R_x A	no product	no product
		R_x C	no product	no product
III	3,6-Dichloro-2-methylaniline	R_x A	6.13 ± 0.02	1.73 ± 0.01
		R_x D	6.15 ± 0.01	1.73 ± 0.01
IV	4,5-Dichloro-2-methylaniline	R_x B	not detectable[c]	not detectable[c]
		R_x C	18.83 ± 0.04	2.72 ± 0.2
V	4,6-Dichloro-2-methylaniline	R_x B	6.37 ± 0.3	1.76 ± 0.01
		R_x D	no product	no product
VI	5,6-Dichloro-2-methylaniline	R_x C	7.73 ± 0.05	2.00 ± 0.01
		R_x D	7.67 ± 0.1	2.02 ± 0.02
	3,4,6-Trichloro-2-methylaniline	R_x A	23.6	8.80
		R_x B	23.6	8.70
		R_x D	23.7	8.80
	4,5,6-Trichloro-2-methylaniline	R_x A	28.2	9.35
		R_x B	28.6	9.25
		R_x C	28.8	9.50

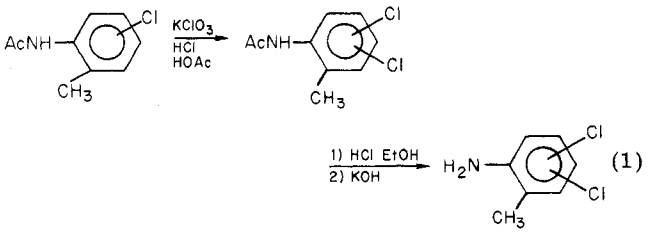
[a] 0.2- to 0.4-μL injections at maximum sensitivity. Solutions were diluted to maintain maximum peaks on scale at attenuation 1. Three injections per sample with retention times given as average and average deviation. Carbowax 1540, 200 °C isothermal. SE-30, 165 °C isothermal. [b] Apiezon J data are given in Table IV. [c] The percentage yields of these isomers were so low (See Table III) that they were not detectable at the conditions set under note *a*.

Table III. Percent Yields for Dichloro- and Trichloro-2-methylanilines[a]

Starting material	Average and average deviation[b]: 5,6-Dichloro	3,4-Dichloro	4,6-Dichloro	4,5-Dichloro	3,6-Dichloro	3,5-Dichloro	3,4,6-Trichloro	4,5,6-Trichloro
4-Chloro		0.27 ± 0.03	58.1 ± 1.7	0.22 ± 0.02			1.55 ± 0.05	1.81 ± 0.06
3-Chloro		25.9 ± 0.60			18.8 ± 0.90	None	0.38 ± 0.06	
5-Chloro	9.26 ± 0.05			46.4 ± 1.30		None		0.60 ± 0.09
6-Chloro	18.1 ± 1.00		None		55.4 ± 1.2		1.25 ± 0.03	0.44 ± 0.20

[a] Percent yields based on 16.35 mmol of starting material. [b] 3-Chloro and 6-Chloro-2-methylanilines, two determinations. 4-Chloro and 5-Chloro-2-methylanilines, three determinations.

not been synthesized. We attempted to synthesize as many of these dichloro isomers as could be produced from the four isomers of monochloro-2-methylaniline, which were commercially available. The experimental procedure was the synthesis of the 2-methylacetanilide derivatives from the four monochloro-2-methylaniline isomers followed by the monochlorination of these derivatives (*2*). Acid hydrolysis and subsequent neutralization of the chlorinated 2-methylacetanilides yielded the dichloro-2-methylaniline isomers.



Two of the isomers could be isolated by recrystallization and were identified by spectroscopic methods. These isomers were 4,6-dichloro-2-methylaniline and 4,5-dichloro-2-methylaniline. Gas chromatographic analyses of the reaction mixtures revealed that both the 5,6-dichloro-2-methylaniline and 3,6-dichloro-2-methylaniline's unsuccessful recrystallizations were hampered because of appreciable concentrations of a companion isomer (See Table II). Since the 5,6-dichloro- and 3,6-dichloro-2-methylaniline mixtures were not recrystallized, two chromatographic nonpolar columns were constructed and used with a commercially available polar column to identify the isomers and calculate their percent yields. The retention times for these three columns are given in Table I

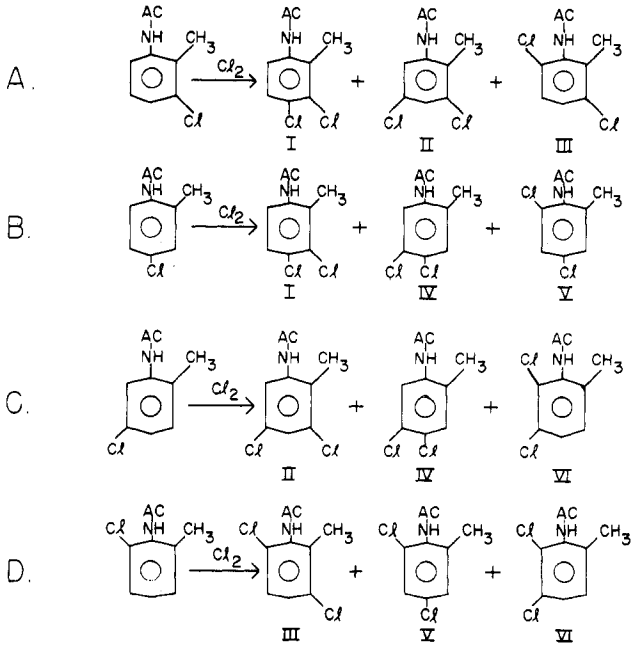


Figure 1. Four reaction schemes

and II with their yields reported in Table III. Table II was constructed as a double check on the retention times given in Table I to make sure a concentration factor was not introducing an erroneous retention time. Table II contains data for two of the trichloro-2-methylaniline isomers (there are a total of four trichloro isomers) which were generated in the

Table IV. Retention Time vs. Dipole Moment

Compound	Dipole moment	Retention time[a]
3,6-Dichloro-2-methylaniline	1.69	6.05 ± 0.00
4,6-Dichloro-2-methylaniline	3.08	6.24 ± 0.03
3,5-Dichloro-2-methylaniline	3.37	
5,6-Dichloro-2-methylaniline	3.66	6.78 ± 0.02
3,4-Dichloro-2-methylaniline	4.37	9.67 ± 0.02
4,5-Dichloro-2-methylaniline	4.59	9.76 ± 0.01
3,4,6-Trichloro-2-methylaniline	3.38	5.90
4,5,6-Trichloro-2-methylaniline	4.73	6.30

[a] Apiezon J, 175 °C isothermal, 0.2- to 0.40-μL injections at maximum sensitivity. Solutions were diluted to maintain maximum peaks on scale at attenuation 1. Three injections per sample with retention times given as average and average deviation.

reactions along with the dichloro isomers.

To add further credence to the identity of these isomers, dipole moments were calculated using group moments from Smyth (*14*). These calculated dipole moments are given in Table IV, and they linearly coincide very closely with the retention times (detector attenuation one) on the nonpolar column, Apiezon J.

Since the 4,6-dichloro and the 3,6-dichloro isomers had very similar retention times, we diluted the sample reaction mixtures in such a manner that 0.2 to 0.4 μL of sample would produce the highest percentage isomers on the chromatograms at maximum sensitivity of the detector. These retention times are shown in Table III and definitely establish a finite time difference between the 4,6-dichloro and 3,6-dichloro isomers.

The directive influence of the AcNH– group over the CH_3–, and Cl– groups is evident in the chlorination of the 3-, 4-, and 5-monochloro-2-methylacetanilides. One can note that in almost every case the highest percentage yield isomer was produced in the ortho or para position to the AcNH– group (see Table III). The only exception to this directive influence of the AcNH– group occurs in the 6-chloro-2-methylacetanilide where 97% of the isomers generated occurs meta to the AcNH– group. Undoubtedly, the directive influence of the AcNH– group is lost in this isomer because of the steric effect of the *ortho*-methyl and *ortho*-chloro groups, e.g., the steric inhibition of resonance (*15*). These bulky ortho groups prevent the coplanarity of the AcNH– group with the benzene ring and inhibit the resonance interaction of the nonbonding pair of electrons on nitrogen with the aromatic ring.

The trichloro isomers, as expected, were generated from the most abundant dichloro isomers produced, i.e., the 4-chloro-2-methylacetanilide produced a 58% yield of the 4,6-dichloro-2-methylacetanilide which, subsequently, was chlorinated to produce 4,5,6-trichloro-2-methylacetanilide and 3,4,6-trichloro-2-methylacetanilide.

Only one dichloro isomer was not produced in the chlorination reactions, the 3,5-dichloro-2-methylacetanilide. Again, this is understandable from the data because of the dominating directive influence of the NHAc– group over that of the CH_3– and Cl– groups.

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