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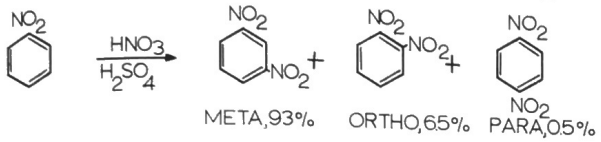
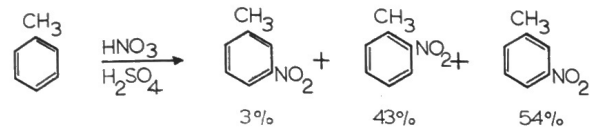
METHODS OF CHANGING ORIENTATION IN ELECTROPHILIC AROMATIC SUBSTITUTION

D. E. PEARSON
Vanderbilt University, Nashville, Tennessee

We all are introduced to the subject of electrophilic aromatic substitution by learning the generalization that electron-withdrawing groups attached to the aromatic nucleus direct *meta* as shown for the nitro group:



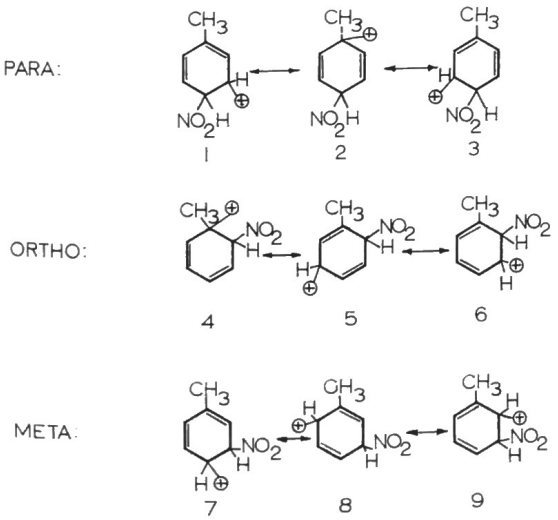
and that electron-release groups, such as the methyl group, direct *ortho* and *para:*



As can be noted, minor amounts of other isomers are formed simultaneously.

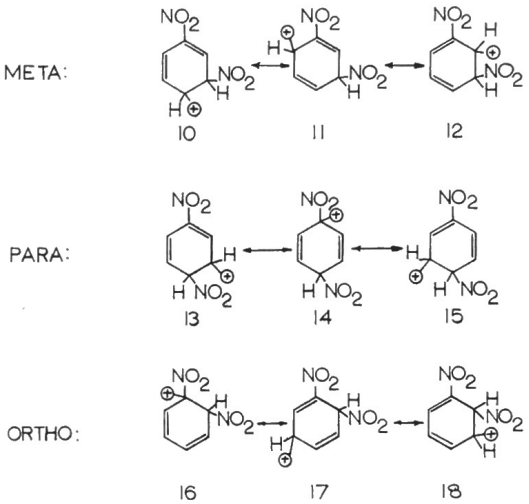
The rationalization of the orientation has been debated for nearly a century, and it has been only recently that a relatively simple explanation has emerged. In electrophilic substitution, a positive ion (or the positive end of a dipolar molecule) attacks the pi electron system of the aromatic nucleus to form a sigma complex. The sigma complex is one of the transition stages through which the reactants pass to form the products. Usually, its formation is rate-determining. It can be isolated in special cases but only under very low temperature conditions.

It probably exists as the free ion as illustrated or as an ion-pair. The relative stabilities of these sigma complexes determine orientation. For example in the nitration of toluene, the following sigma complexes are formed:



It will be noted that only in the case of the canonical forms (*2*) and (*4*) is the positive charge located at a tertiary carbon atom. Therefore, these forms contribute much more than any others and favor the formation of *ortho-* (because of form (*4*)) and *para*-substitution (because of form (*2*)). What's more, the rates of substitution are accelerated because of the favorable stabilization features of (*2*) and (*4*).

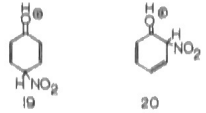
In the case of the nitration of nitrobenzene, the following sigma complexes are formed:



Here we find no factors for stabilization of positive ions. Indeed, canonical forms (*14*) and (*16*) are probably non-existent as contributors to the stability of the sigma complex because the positive charge is located at a position adjacent to a positive nitrogen atom. Therefore, *ortho-* and *para*-nitration of nitrobenzene does not take place to any great extent for the reason that only two relatively unstable canonical forms contribute to the stabilization of either the *ortho* or *para* sigma complex. The *meta* isomer has three canonical forms which favor *meta* over *ortho, para*-substitution. Even in this case, however, the three canonical forms (*10*), (*11*), and (*12*) are not comparable to forms (*2*) and (*4*) in stabilization of the positive charge. Therefore, nitrobenzene is nitrated more difficultly than toluene.

Another feature of orientation becomes clear from this theory of substitution. Although alkylbenzenes give almost statistical distribution of substitution between the *ortho* and *para* positions (i.e., 66% *ortho,* 33% *para*), other benzenes with hydroxyl, amino, and other similar groups give almost 100% *para*-substitution. The reason is that another *para*-quinoid canonical form contributes to the stability of the sigma complex.

This form has a greater contribution than any of the forms (*1*) through (*18*) mentioned previously. It (*19*) has greater stability than the *ortho*-quinoid canonical form (*20*) probably for the same reason that *p*-benzoquinone is more stable than *o*-benzoquinone.



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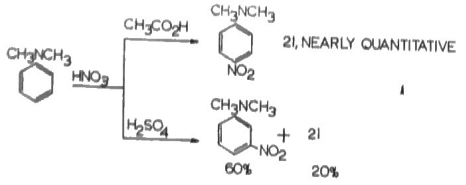
In the *p*-quinoid form the substituent itself participates directly in delocalization of the charge as shown in (*19*). Thus nitration of phenol gives mainly *para*-nitrophenol.

The purpose of the discussion is not to discuss orientation per se but to explore means of changing normal orientation. We can ask ourselves: Are the rules of orientation immutable? Are there methods of obtaining isomers of difficult accessibility? It has been more or less a hobby of the author to collect methods of changing orientation not only to keep research records complete but also to furnish illustrations for teaching.

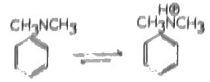
It is quite gratifying to find that all new methods which have come to the attention of the author seem to fit well into the categories which were listed a decade ago. They are now relisted with the most recent illustrations.

(1) *Modification of the Substituent.* This method is obviously the most direct one for changing orientation. The substituent controls the orientation; therefore, we should attempt to change the substituent. The substituent can be changed in two ways:

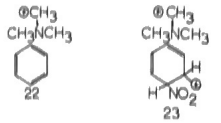
a. *By changing the environment.* It must be remembered that electrophilic substitution involves the attack of positive ions or particles. These species are obtained only in acid or Lewis acid solutions. Therefore, we are limited in changing the substituent from one with basic properties to one with neutral or acidic properties, not the reverse. In other words, we are limited in changing orientation from *ortho- para* substitution to *meta*, not the reverse. A good example in changing the substituent by changing the medium is shown:



In acetic acid, substitution occurs through the free base. In concentrated sulfuric acid, the dimethylamino group is converted to the salt and substitution occurs through this intermediate:



Indeed, the surprising fact is that orientation is not 100% *meta* and might suggest that the dimethylaniline is incompletely converted to its salt. Ridd's work [1]* supplies information on this point. The quaternary salt (*22*) in which a formal, positive charge must reside at all times on the nitrogen atom gives 88% *meta* and 11% *para* nitration.



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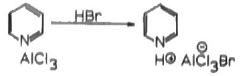
Apparently a positive charge is not sufficiently strong to eliminate the canonical form (*23*) which would lead to *para*-substitution. Other examples corroborate the surmise that we will reach a limit in changing orientation in the anilines. Gorvin [2] obtained 60% *meta*-substitution in the bromination of dimethylaniline in concentrated sulfuric acid using bromine and silver sulfate as the brominating agent. The Vanderbilt group has contributed some information to this problem. We were attempting to substitute into pyridine, a most difficult nucleus to substitute, because the nitrogen atom imbedded in the ring is protonated or converted to a Lewis salt under electrophilic conditions. With $AlCl_3$ our yields in bromination seemed to approach a maximum of 50% 3-bromopyridine based on pyridine. We found to our surprise that the hydrogen bromide released was the culprit forming a new salt (*25*) which was so deactivated that no substitution could be brought about [3].



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When (*25*) was made by passing HBr into (*24*), no bromination at all could be discerned. Thus the theoretical acid $HAlCl_3Br$ was more powerful than $AlCl_3$ in deactivating pyridine. It was our conclusion that we had at hand the most powerful acid that could be used for protonating aromatic nuclei and thus bring about the greatest change from *ortho, para-* to *meta-* orientation. The results in brominating aromatic amines are shown in Table 1.

Even with this powerful acid, only 50% *meta*-substitution was obtained with aniline. However, if a second substituent is added which blocks one of the normal positions of substitution and aids in directing to the abnormal position, very good yields of *meta*-substitution can be obtained as shown with the last five exam-

*Numbers in brackets refer to Literature Cited.

Table 1

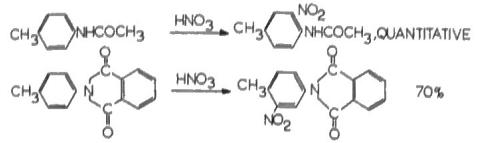
Halogenation of aromatic amines [4].

Aniline	*Halogen*	*Aniline product*	*Yield %*
Unsubstituted	Br_2	3-Bromo	50
N,N-Dimethyl-	Br_2	3-Bromo	60
p-Bromo-	Br_2	3, 4-Dibromo	77
p-Chloro-	Cl_2	3, 4-Dichloro	71
p-Methyl-	Cl_2	3-Chloro-4-methyl	82
p-Bromo-	Cl_2	3-Chloro-4-bromo	71
o-Chloro-	Br_2	2-Chloro-5-bromo	73

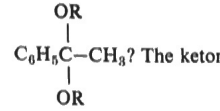
ples of Table 1. Without the use of the strong acid $HAlCl_3Br$, all of the substitutions would have occurred in the 2-position of the above anilines.

It would seem that we should discuss change of orientation of other families of compounds at this time, but we will find that many of the other groups fall into a different category of classification discussed in a later section.

b. *By derivatization.* Alteration of the substituent can be brought about not only by adjusting the acidity of the medium but also by derivatization prior to introduction into the medium. It is a well-known method but one that has not been exploited as completely as it should be. The nitration of aniline derivatives serves as one example:



The phthalyl group not only deactivates the position *ortho* to the nitrogen atom by electron-withdrawal but also hinders the approach of the reagent to the *ortho* position by its bulk. To extend this method, it would seem fruitful to study trifluoroacetyl derivatives or other derivatives with strong electron-withdrawing groups attached directly to the substituent. Furthermore, there remains the possibility of changing a substituent by derivatization from a *meta* to an *ortho-para*-directing group. Is it known, for example, what the orientation is in the ketal derivatives of acetophenone,



meta-substitution.

(2) *Modification of Reagent Activity.* The second method of altering orientation is to change the character of the attacking species. We have, of course, the general rule that the more reactive the reagent the greater the tendency to substitute in a statistical manner. No reagent that powerful has been found. Indeed, the method is rather limited in its ability to accomplish dramatic changes in orientation. One of the approaches used is to complex the attacking species with molecules of strong solvating powers such as nitromethane or acetonitrile to decrease activity and enhance selectivity. The limitations can be seen in the results of Table 2:

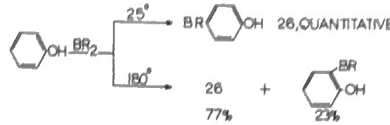
Table 2

Nitration of toluene at 25° [5a].

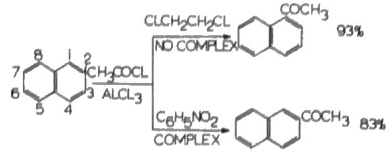
Solvent	% ortho	% meta	% para
H_2SO_4	56	5	38
$(CH_3CO)_2O$	61	2	37
$(CH_3)_4SO_2$	62	3	35
Neopentyl nitrate in PPA[5b]	49		51

For nitration at least very little difference exists between solvents of quite different polarity.

Another approach is to use a higher temperature for less selectivity (or vice versa):



As a corollary to altering reagent reactivity it is also possible to alter the size or bulk of the reagent and thus direct substitution to a more open position. The classical example is the acylation of naphthalene [6]:



But also some effect can be brought about by the solvent with simpler reagents than acetyl chloride. Chlorination of toluene in hydroxylic solvents gave about 60% *ortho-* and 40% *para*-chlorotoluene but in non-hydroxylic solvents such as nitromethane and acetonitrile gave about the reverse ratio [7]. Apparently, the chlorination reagent is more bulky in the latter solvents.

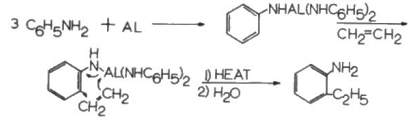
(3) *Substitution from the Position of the Substituent.* The third method of changing orientation has become of growing interest, and we find many recent examples of its application. Before enumerating a few examples we should make clear that most of them refer to *ortho-para* directing groups. The statistical ratio is 66% *ortho* and 33% *para*. If less *ortho* and more *para* substitution is obtained, the change is attributed to steric repulsion of the reagent from attack at the *ortho* position. It is a quite significant factor as can be judged from the drop-off of *ortho*-substitution in the alkylbenzene family shown in Table 3.

Table 3

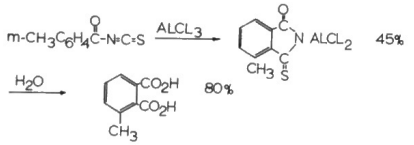
Nitration of alkylbenzenes [8].

Substrate	% ortho	% para
Toluene	58	37
Ethylbenzene	45	49
Isopropylbenzene	30	63
tert.- Butylbenzene	16	73

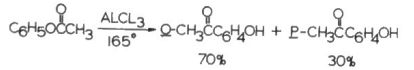
If *ortho* substitution is more than 66%, it is clear that some unusual factor is coming into play. However, if the steric factor lowers the *% ortho* and the unusual factor increases the *% ortho*, it is more difficult to separate the two effects. The unusual factor is simply that the reagent makes its attack on the benzene ring from the position of the substituent. The reagent may be attached to the substituent by a covalent bond or by weak coordination forces. The first example is undoubtedly the most important of this group [9].



This reaction belongs to the group of cyclic electron shift mechanisms and has made available a host of *ortho*-alkylated and 2,6-dialkylated anilines and phenols. An even clearer example of the attack from the *ortho* position is the preparation of phthalic acid compounds [10]:



The Fries rearrangement tends to give more *ortho* substitution for the same reason [11].



High temperature invariably favors the *ortho* isomer.

The effect of weaker attachment to the substituent can be seen in Table 4 [12].

Table 4

The nitration of methyl β-phenylethyl ether at 25°.

Reagent	% ortho	%-meta	% para
$HNO_3H_2SO_4$	31	10	59
HNO_3	40	7	53
HNO_3, CH_3NO_2	41	3	56
HNO_3, $(CH_3CO)_2O$	65	3	32
$CH_3CO_2NO_2$, CH_3CN	66	4	30

Evidently in the last two examples of Table 4, acetyl nitrate tends to form a weak coordination bond with the side chain and makes its attack from this position. Another example of the unusual effect of acetyl nitrate is found in the nitration of cyclopropylbenzene which gives 80% *o*-nitrocyclopropylbenzene [13], a most striking amount of *ortho* substitution for ordinary coordination bonding. Other examples of this effect have been noted particularly in the substitution of phenol [14]. Kovacic probably has considered the *ortho/para* ratio in greatest detail as shown partly in Table 5 [15].

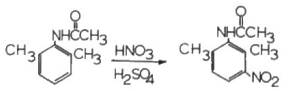
Table 5

Ortho/para ratios in electrophilic aromatic Substitution.

	Mercuration in perchloric acid	Mercuration in acetic acid	Methylation in nitromethane
Toluene	0.2	0.3	1.6
Chlorobenzene	0.5	0.6	1.7
Anisole	1.2	0.1	1.9

The most noteworthy feature of this table is that the coordination of the reagent seems to be dependent on the solvent. In perchloric acid, the mercuric ion gives considerable *ortho* substitution in anisole, suggesting coordination with the methoxyl group but in acetic acid very little mercuration takes place in the *ortho position*. Methylation and indeed other alkylations yield such high *ortho/para* ratios that a coordination phenomenon may be involved.

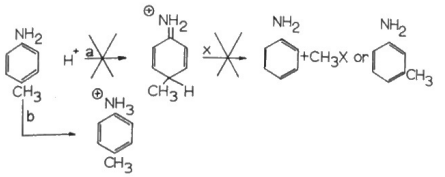
(4) *Steric Inhibition of Resonance in Controlling Orientation.* This method is most specific, requiring bulky groups attached in a position adjacent to the substituent that controls orientation. The most classical example is the nitration of 2,6-dimethylacetanilide [16]:



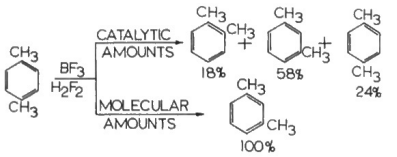
Normally, one would expect to observe nitration *para* to the acetamino position. The reasoning behind the actual fact that *meta* substitution is obtained is that the acetamino group is tilted out of the plane of ring by the two methyl groups. The acetamino group becomes more basic because of steric inhibition of resonance between the nitrogen atom and the ring, the acid protonates the acetamino group, and the positively charged group directs *meta*. The reasoning must be correct because if a more acidic residue such as the benzenesulfonyl group is attached to the nitrogen atom rather than the acetyl group, this compound nitrates to the extent of about 80% in the *para* position. The benzenesulfanilide cannot be protonated by the acid and thus is free to carry out the normal activation process of the *para*-position.

(5) *Thermodynamic Control Vs. Kinetic Control of Orientation.* We come to the fifth, last, and most extensive method of control of orientation. Up to now, we have restricted our discussion for the most part to irreversible reactions such as nitrations, acylations and substitutions in aniline rings. Irreversible reactions are those in which the reagent and the benzene ring form a bond stabilized by resonance. Among reversible reactions, in which no additional resonance takes place between the ring and the attached group are alkylations, protonations, iodinations. Bromination seems to be intermediate, being somewhat reversible probably because only weak resonance interaction takes place between the benzene ring and bromine atom:

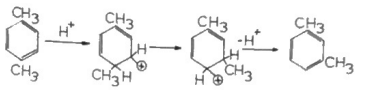
It is a curious fact that all substitutions including alkylation are irreversible with anilines. The rationale brings out the most important feature of reversibility. In order for an aromatic substitution to be reversible protonation must take place at the position of group attached:



In the case of anilines, the proton attaches itself to the nitrogen, and it is most difficult, if not impossible, to force the same proton or a second proton on to the carbon attached to the methyl group. With the hydrocarbons we have no such problem of localization of the proton and thus thermodynamic control is quite feasible [17]:



With catalytic amounts of HBF_4, a mixture closer to kinetic control is obtained, i.e., closer to the orientation from direct substitution. On the other hand, with large amounts of catalyst, a completely *meta*-substituted compound is formed. We would like to make a simplifying statement: under the mildest conditions where the fewest protons are present, typical *ortho-para* substitution predominates, which we call kinetic control. Under strong conditions with maximum concentrations of protons, *meta* substitution predominates, which we call thermodynamic control. It is logical to expect these results because alkyl groups orient *ortho-para*. In kinetic control the second alkyl group is directed to these positions. In thermodynamic control, the proton is directed to the same positions which then brings about migration of the alkyl group by a Wagner-Meerwein shift mechanism:



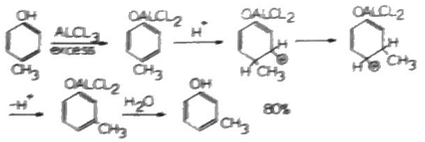
It is a dynamic situation with protonation occurring at all positions but most frequently at the *ortho-para* ones. The frequency factor decides the point of equilibrium.

Even at the risk of exposing the reader to repetition, we will state the conditions for kinetic and for thermodynamic control. Aluminum chloride in nitromethane seems as good as any catalyst system for kinetic control—just so the moderating solvent, nitromethane, is present. For thermodynamic control two systems, supplementary to each other, are recommended. For aromatic hydrocarbon rearrangement which is relatively facile boron trifluoride in liquid hydrogen fluoride seems to be the preferred reagent. In our opinion it is not the strongest protonic acid but does serve to furnish a large pool of protons from the liquid hydrogen fluoride. For alkyl group migration in phenols, ketones, aldehydes, esters or for alkyl group substitution into aniline, aluminum chloride and its co-catalyst, hydrogen chloride, seems to be the best catalyst for thermodynamic control. It is an extremely powerful acid, if not the most powerful protonic acid known. The only drawback is that a large excess pool of protons can be made available only under pressure. Any hydrogen chloride in excess of the equivalent amount of aluminum chloride simply passes out of the system. We also have had as much success with aluminum bromide, made in situ from aluminum granules and bromine, to which the substrate is added followed by passing through hydrogen bromide to the saturation point.

The methyl group in aromatic compounds is unique in that very little disproportionation takes place under sigma complex conditions—ethyl, and particularly *tert*-butyl groups are removed and transferred to other molecules. This phenomenon is also logical. They form more stable carbonium ions. Furthermore, since alkyl groups are activating, i.e., increase the electron density of the ring system, the first alkyl group should be the most difficult to substitute—the last the easiest so long as a steric problem is not encountered. In other words the ease of substitution is in the order penta > tetra > tri > di > monomethylbenzene. Indeed, we are now discussing one of the most important drawbacks of alkylation: the tendency to polyalkylate under conditions for monoalkylation. We will describe such a problem shortly. But before discussion of the subject of hydrocarbon orientation is completed, the situation with regard to the formation of cymene (isopropyltoluene) should be discussed. It is the best understood of all hydrocarbon preparations. Apparently under the very mildest conditions (aluminum chloride in acetonitrile), the isopropylation of toluene yields 63% *o*-, 25% *p*- and about 12% *m*-cymene [18]. No one has obtained less *m*-cymene and quite possibly the above figures represent direct substitution. To proceed in the opposite

direction, i.e., to obtain the most *meta*, we have turned to the liquid hydrogen fluoride—boron trifluoride system which is particularly suitable for isomerizations which take place with ease. After about one hour at —70°, *p*-cymene was rearranged to *m*-cymene of excellent quality in about 82% yield.

The problem of changing orientation in cresols is a difficult one. Boron trifluoride-hydrogen fluoride fails completely in the attempted rearrangement of *p*- to *m*-cresol. On the other hand, aluminum chloride-hydrogen chloride with p-cresol at about 120° gives a good yield of cresols containing 80% *m*-cresol and 20% *p*-cresol as shown:



Previous attempts to run this rearrangement led to a product of 60% *m*- and 40% *p*-composition [19], but no adjunct hydrogen chloride had been passed into these systems. Indeed, for a period, we believed that passing hydrogen chloride through the *p*-cresol-aluminum chloride complex was the limit of our capacity to supply protons to the system and thus an 80% *m*-, 20% *p*-cresol was the closest to thermodynamically-controlled product we could get. It then occurred to us to liquify hydrogen bromide in the *p*-cresol-aluminum chloride complex and run the reaction under autogenous pressure at about 100°. A product was obtained in good yield which was essentially pure *meta*-cresol. Our objective had been achieved, albeit under extremely strenuous conditions. On the other hand, the higher alkylated phenols were converted easily and almost quantitatively to the thermodynamically-controlled isomers by simply passing hydrogen chloride through the aluminum chloride complexes. The following conversions were made:

3,4- or 2,4- or 2,5-Xylenol→ 3,5-Xylenol
2,4,5- or 3,4,5- or 2,4,6-Trimethylphenol→2,3,5-Trimethylphenol
2,3,4,6-Tetramethylphenol→2,3,5,6-Tetramethylphenol

It should be noted that the methyl group in the *para*-position is the most susceptible to migration. Therefore the proton must attack this position preferentially. From a synthetic viewpoint, this is a most fortunate situation. With kinetic control conditions *para*-alkylation is obtained; with strong acidic conditions *para*-substitution is not obtained. Practically any methylated phenol is available therefore by proper choice of conditions.

p-Bromophenol is less susceptible to the attack of protons (because the bromine atom deactivates the ring). But we were able to rearrange this compound to 50% *meta*-bromophenol. Indeed, we showed that in the bromination of phenol under sigma complex conditions, the bromine first enters the *para*-position and then migrates (to the extent of 50%) to the *meta*-position. We next attempted to monomethylate phenol under sigma complex conditions. The results are shown in Table 6:

Table 6

The products of the reaction of phenol (0.2 mole) with methyl bromide (0.2 mole) in the presence of $AlCl_3$ (0.4 mole) and hydrogen chloride.

Phenol	32%	2,4- and 2,5-Xylenols	2%
o-Cresol	Trace	3,5-Xylenol	27%
m-Cresol	6%	2,3,5-Trimethylphenol	24%
p-Cresol	2%	2,3,5,6-Tetramethylphenol	7%

One can see the difficulty of confining alkylation to a single product. However, most of the products are those of thermodynamic control.

A last example of alkylation was quite interesting. We had shown that complexation of quinoline with aluminum chloride diverted substitution into the benzenoid ring giving usually 5-substitution in halogenation [20]. In ethylation of quinoline under the same conditions we isolated an ethylquinoline in about 20% yield which had constant physical properties among fractions of a carefully distilled product. The refractive index, b.p., and gas chromatography all suggested a pure compound which we believed to be 5-ethylquinoline. However, gas chromatography of this material using a Bentone-34 substrate, a stationary phase which shows excellent properties for separating isomers, showed two peaks. It turned out that the material was actually 60% 5-ethylquinoline and 40% 7-ethylquinoline with a trace of 6-ethyl also present. We should have suspected this result from the beginning because alkylation with large amounts of aluminum chloride should give some products of thermodynamic control. The 7-ethylquinoline is this product, the 5-ethyl is the product of kinetic control.

All methods of changing orientation have now been listed and one can see that the over-all picture is quite complex but nevertheless manipulative. Means are available for changing a group from an *ortho* and *para*- to a *meta*-director. Solvents can be chosen to bring about substitution in more open positions. Exclusive *ortho* substitution can be brought about if the reagent can be attached or coordinated to the substituent. And, lastly, for reversible reactions, the choice of kinetic or thermodynamic conditions is a powerful tool in the manipulation of orientation.

In conclusion, we do not wish to convey the impression that methods of changing orientation fall into five and only five categories. They are merely convenient vehicles for discussion and they are limited by the scope of one man's reading and experience. Casting into the unknown and into the future, we see at least one area of promise. If we could run substitutions on aromatic molecules in excited states (activated, for example, by light absorption) we might find some unusual orientations. The difficulty, of course, is to maintain finite concentrations of excited molecules during their exposure to the reagent.

And who can say that other methods will not be discovered?

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NEWS OF TENNESSEE SCIENCE

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DONALD E. PEARSON, professor of Organic Chemistry at Vanderbit University and author of the foregoing article, is on leave spring semester for research on the Friedel-Crafts reaction and completion of a book on the synthesis of organic compounds.

The National Science Foundation has awarded the University of Tennessee a $4,000 research grant for a study of "Matrix Representation of Topological Semigroups," a phase of algebra. Dr. Dennison R. Brown, assistant professor of mathematics at UT, is director of the study. He is being assisted by Daniel R. McCord, UT graduate student in mathematics.

Samuel L. Meyer, president of the Tennessee Academy of Science in 1950, has accepted the presidency of Ohio Northern University, Ada, Ohio, effective September 1. For a number of years Dr. Meyer was head of the University of Tennessee Botany Department. He goes to Ohio Northern from the University of the Pacific, where he was academic vice president.

Five grants totaling $170,029 have been presented to the University of Tennessee for continuation of research in four areas and initiating study in another. The largest grant, from the U. S. Air Force, amounted to $90,000 for an extension of an experimental study of infrared spectral line shapes. The research is under the direction of Dr. A. H. Nielsen, head of the University's physics department and dean of the College of Liberal Arts. Two National Institutes of Health grants support continuation of studies in the Department of Chemistry and graduate training in psychiatry. Under these grants Dr. D. A. Shirley, Department of Chemistry, will receive $9,396 to continue to direct research on "Derivatives of Azacarcinogens as Anticancer Agents." The NIH has awarded the UT Memorial Research Center $43,833 to establish a year's additional graduate training in psychiatry under the direction of Dr. John H. Wolaver and Dr. James A. Burdette. A $22,800 two-year grant from the National Science Foundation will require Dr. Gordon E. Hunt, Department of Botany, to spend a year at the U. S. Department of Agriculture Laboratory, Ithaca, New York. The study, to be completed at UT, concerns "The Metabolism of Canavanine and Alpha-Amino, Delta Hydroxy Valeric Acid in the Jackbean and in Other Legumes." Research on infrared feasibility for nondestructive testing, conducted by Dr. W. E. Deeds, Department of Physics, has been extended for an additional nine months with $4000 from Oak Ridge National Laboratory.

A $42,744 contract for research in biology has been awarded Austin Peay State College by the Tennessee Valley Authority. The grant is for use by the Department of Biology for studying certain biota of Land Between the Lakes Park in Tennessee and Kentucky. Dr. Haskell C. Phillips, chairman of the APSC Department of Biology, will direct the study. Others included in the study are Dr. William H. Ellis, associate professor of biology, who will study the higher vascular

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