[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY OF THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

STUDIES ON THE DIRECTIVE INFLUENCE OF SUBSTITUENTS IN THE BENZENE RING. IV. THE PARTIAL BROMINATION OF DERIVATIVES OF ANILINE[1]

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In Part II[3] it was shown that the addition of bromide-bromate solution in amount insufficient for complete tribromination to an acidified aqueous solution of aniline gives precipitates of tribromo-aniline, the yields being less than the relative amounts of bromine solution added, and corresponding to a smooth curve. This curve is a function of the relative velocity constants of bromination in the three positions which are substituted. Similar curves were found when the same method was applied to certain derivatives of aniline for example, *o*- and *p*-aminobenzoic acids.

In the continuation of this investigation the partial-bromination curves (relative yield of highest brominated product, z or y, plotted against the relative amount of bromine solution added, r, compared with the calculated requirement) of several additional aromatic amino compounds have been obtained. This was done primarily for the purpose of calculating the results of competition experiments.[4] By means of the latter the relative rates of bromination of these compounds were compared in order to estimate the directive influences of the other substituents beside the amino group.

With a few exceptions, to be discussed below, all *m*-amino compounds were found to have exactly the same curve as that of aniline. The curve is determined only by the *ratios* of the velocity constants in the three available positions (2, 4 and 6). The identity of curve indicates, therefore, that while the other substituent may affect greatly the absolute rate of bromination, it affects the rate in each of the three positions to precisely the same extent, so that their ratios are unchanged. Similarly, *o*- and *p*-amino compounds, which receive only two molecules of bromine,[5] exhibit two other curves, respectively, which are the same for members of each class. Thus, *p*-bromo-aniline, *p*-aminobenzoic acid, *p*-toluidine, etc., all have the same curve, although the other substituent may be a *meta* orienting group (and through coöperation with the influence of the amino group in such cases, accelerate substitution), or an *ortho-para*

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[3] Francis, Hill and Johnston, THIS JOURNAL, **47**, 2211 (1925).

[4] Ref. 3, p. 2220.

[5] Francis and Hill, THIS JOURNAL, **46**, 2498 (1924).

orienting group (and because of opposition, retard bromination). These observations simplify considerably the study of amino compounds, since the curves are used continually in the calculation of the competition experiments. They also offer hope of simplifying in one respect the explanation of directive influence, since they show that the latter can be considered as distributed symmetrically around the ring.

Because of their general application, the three curves mentioned merit careful mathematical analysis. The aniline or "*meta*" curve was shown in the previous paper to correspond with the following relation between the velocity constants of bromination in the three positions, the tie indi-

$$\widehat{K_1 : K_2} : K_3 = \widehat{1 : 1} : 1.13 \qquad (1)$$

cating simultaneous substitution by bromine in two of the positions. The equation for the curve is

$$\left(\frac{2 - 3r + z}{2}\right)^{1.13} + \frac{3 \times 1.13}{2}(r - z) + z = 1 \qquad (2)$$

in which z is the relative yield of tribromo product, and r is the relative amount of bromine solution added.

In the case of the "*para*" curve

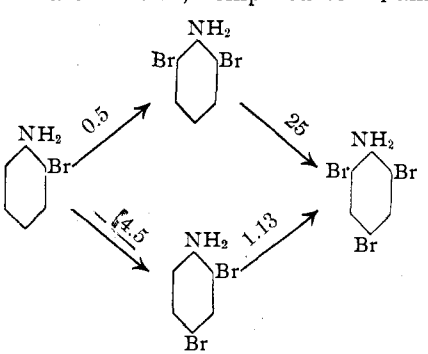
$$K_1 : K_2 = 1 : 1.9 \qquad (3)$$

the equation is

$$(1 - 2r + y)^{1.9} + 2 \times 1.9\,(r - y) + y = 1 \qquad (4)$$

y being the relative yield of dibromo product.

The "*ortho*" curve does not have so simple a mathematical analysis, no single value for the ratio of constants holding throughout the curve, although the latter was perfectly reproducible in all cases. The explanation found is that the bromine goes first, mostly in the 4 position (with respect to the amino group), but partly in the 6 position, as in the following scheme in the case of *o*-bromo-aniline, four velocity constants being involved (the constants are relative, compared to K_1-aniline).



Two of the constants, 1.13 and 25, were obtained directly by competition experiments with other suitable compounds, using 2,4- and 2,6-dibromo-

aniline, respectively. The sum of the other two, 5, was obtained in the same way with *o*-bromo-aniline itself. To complete the scheme, only the ratio of these two, 9, was necessary; and this single arbitrary constant could be obtained from the curve by trial values. The equation for the curve was derived as follows.

Let us start with M moles of *o*-bromo-aniline and B moles of bromine in a total volume V; we shall find it convenient to write, in place of B, $2Mr$, where r is a fraction denoting the relative amount of bromine taken (B) compared with that which would be required ($2M$) for complete conversion of the mono- to tribromo-aniline. Let x' and x'' be the fractions of the *o*-bromo-aniline which have been substituted in Positions 6 and 4, respectively, the velocity constants being K_1' and K_1''; and let y' and y'' be the relative yields of tribromo-aniline formed by way of 2,6- and 2,4-dibromo-aniline, respectively, the second velocity constants being K_2' and K_2''. It will be convenient to employ the following ratios of constants: $m = K_1''/K_1'$; $a = K_2'/K_1'$; and $b = K_2''/K_1'$. Then,

$$\mathrm{d}(Mx')/\mathrm{d}t = (K_1'M^2/V)(1 - x' - x'')(2r - x' - x'' - y' - y'') \quad (5)$$
$$\mathrm{d}(Mx'')/\mathrm{d}t = (K_1''M^2/V)(1 - x' - x'')(2r - x' - x'' - y' - y'') \quad (6)$$
$$\mathrm{d}(My')/\mathrm{d}t = (K_2'M^2/V)(x' - y')(2r - x' - x'' - y' - y'') \quad (7)$$
$$\mathrm{d}(My'')/\mathrm{d}t = (K_2''M^2/V)(x'' - y'')(2r - x' - x'' - y' - y'') \quad (8)$$

Dividing (6) by (5), and integrating,

$$\mathrm{d}x''/\mathrm{d}x' = K_1''/K_1' = x''/x' = m \text{ (Wegscheider's principle)} \quad (9)$$

Dividing (7) and (8) by (5), and combining with (9),

$$\frac{\mathrm{d}y'}{\mathrm{d}x'} = \frac{K_2'(x' - y')}{K_1'(1 - x' - x'')} = \frac{a(x' - y')}{1 - x' - mx'} \quad (10)$$

$$\frac{\mathrm{d}y''}{\mathrm{d}x'} = \frac{K_2''(x'' - y'')}{K_1'(1 - x' - x'')} = \frac{b(mx' - y'')}{1 - x' - mx'} \quad (11)$$

Integrating (10),

$$y' = \frac{a}{a - 1 - m}\left[x' - 1/a - C(1 - x' - mx')^{a/(1+m)}\right] \quad (12)$$

When $x' = 0$, $y' = 0$, so that $C = -1/a$

$$y' = \frac{ax' - 1 + (1 - x' - mx')^{a/(1+m)}}{a - 1 - m} \quad (13)$$

Integrating (11) similarly,

$$y'' = \frac{m[bx' - 1 + (1 - x' - mx')^{b/(1+m)}]}{b - 1 - m} \quad (14)$$

The observed yield (y) of tribromo-aniline is $y' + y''$. By substituting x (the fraction of the *o*-bromo-aniline which has received at least one bromine atom) for $x' + x''$, and the numerical values of the constants as found by observation and trial, $m = 9$, $a = 50$, $b = 2.26$, $x = (1 + m)x' = 10x'$,

$$y = \frac{5x - 1 + (1 - x)^5}{40} + 1.16\,[1 - 0.226x - (1 - x)^{0.226}] \quad (15)$$

Equation 15 is to be combined with the experimental condition, $x + y = 2r$, for, when the observation is made, all the bromine has been consumed.

The high velocity constant of bromination of 2,6-dibromo-aniline is surprising, especially considering that the new bromine atom must enter a position *meta* to two other bromine atoms; but it is consistent with the first velocity constant of *o*-bromo-aniline itself, being nearly the square of the latter, showing that the second *ortho* bromine has nearly the same effect as the first (5-fold acceleration).

In view of the identity of the curves for *o*-amino compounds, it may be assumed that they are all brominated according to the same scheme, with the four constants in the same ratio to one another, but with the absolute values changed. Thus, from the combined first constant of anthranilic acid, 23, it might be predicted that 2-amino-3-bromobenzoic acid (the analog of 2,6-dibromo-aniline in the bromination of anthranilic acid) would be brominated with a velocity constant of 115 (five times the combined first constant of the latter).

The relative simplicity of the *para* curve is due probably to the fact that the two available positions are equivalent.

The symmetrical distribution, around the ring, of directive influence of substituents is illustrated also in such compounds as 1,2-xylidine-4, in which one methyl group is *meta* to the amino group and, as in *m*-toluidine, has no effect upon the partial bromination curve, and the other methyl group is *para* to the amino group. Two molecules of bromine are consumed, and the curve is identical with that of *p*-toluidine. The absolute rate is slightly greater than that of *p*-toluidine to about the same extent that the rate for *m*-toluidine exceeds that of aniline, as might be expected. 2-Aminotoluene-4-sulfonic acid follows the *ortho* curve because it is a derivative of *o*-toluidine, the *m*-sulfonic group, as in *m*-aminobenzenesulfonic acid, having no effect. 1,4-Xylidine-2, however, which should follow the *ortho* curve, fails to do so, the curve being distinctly higher. No reason is offered as yet for this exception.

A fourth partial bromination curve is exhibited by compounds having two amino groups *meta* to each other (*o*- and *p*-diamines are oxidized to quinoid forms or dyes under these conditions). This is a straight line,

$$y \text{ (or } z) = r \qquad (16)$$

indicating simultaneous substitution of all the bromine. As suggested in a previous paper,[6] the reason for this is probably the intermediate substitution by bromine of all four amino hydrogen atoms. Three examples were tried, *m*-phenylenediamine, 2,4-diaminotoluene and 2,4-diaminochlorobenzene. With each of the compounds mentioned, the bromine must be added with caution to avoid oxidation, possibly because of the oxidizing tendency of the superfluous side-chain bromine. The solution must be strongly acid and ice-cold. The same straight line would represent, obviously, the partial bromination of compounds, such as 2-amino-5-

[6] Ref. 5, p. 2502.

nitrotoluene, which react with only *one* molecule of bromine, but these are not included in the tables.

m-Aminophenol has a unique curve, as might be expected because of its two active but different directing groups.

Although the generalizations of this paper have been found to hold for 34 amino compounds, the three nitro-anilines are conspicuous exceptions. In each isomer the last bromination is much slower than the earlier ones; that is, no end product is formed until the preceding substitutions are almost complete. The curve consists practically of only a straight line starting at the one-half point for the *ortho* and *para* isomers, and at the two-thirds point for *m*-nitro-aniline. This stepwise type of curve is

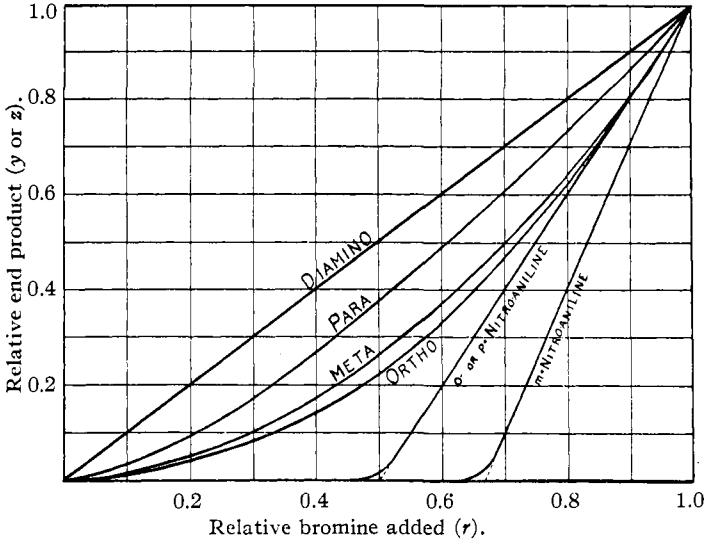


Fig. 1.—Partial bromination. Derivatives of aniline.

characteristic of phenolic compounds rather than amines. The phenomenon is the more remarkable since the three nitrophenols all have curves of the gradual type characteristic of amino compounds (but not identical curves). It would seem that the nitro group reverses in some peculiar way certain properties of the amino and hydroxyl groups. *m*- And *p*-nitromethylanilines likewise show stepwise bromination.

Four representatives of the formula C_6H_5NHR, namely, methyl-, ethyl- and benzylaniline, and phenylglycine, which are tribrominated quantitatively, have also been studied. They do not give satisfactory curves because their intermediate bromination products are difficultly soluble, and the end products oily (except phenylglycine) and not precipitated quantitatively. No definite conclusions could be drawn as to the shapes of their curves, and they are not included in the tables.

The typical partial bromination curves are shown in Fig. 1. The *ortho* and *meta* curves are near together, but distinctly different. Even if they had coincided, the fact would have no significance, however (as it would in the case of *ortho* and *para*), because one curve represents three stages of bromination and the other only two.

Experimental Part

The compounds studied were all best grade products from the Eastman Kodak Company. Their purity was tested by titration[5] in dilute acidified aqueous solution with bromide-bromate solution. Within experimental error (0.5%) all were brominated according to theory, *meta* compounds reacting with three molecular equivalents of bromine, *ortho* or *para* with two, and higher substituted derivatives with the number corresponding to the number of positions *ortho* and *para* to the amino group which were not already substituted. The "highest brominated product" was thus considered to be the one with bromine substituted in all such positions.

In its simplest form, the method of obtaining partial-bromination curves was to add bromide-bromate solution in insufficient amount to the acidified solution containing one millimole of the amine, filter out the precipitate in a Gooch crucible, dry and compare its weight in milligrams with the molecular weight of the product. There are two principal sources of error; (1) the highest brominated product may not be completely insoluble; (2) an incompletely brominated product may be partly precipitated. To correct for these errors it was usual to add to the filtrate an excess of bromide-bromate solution, to titrate this excess with thiosulfate solution, and to filter, dry and weigh the new precipitate. The method of calculation is illustrated best by an example.

Two millimoles of *p*-aminophenylacetic acid (which theoretically requires 4 millimoles of bromine) was dissolved in water to which was added 3 cc. of 50% sulfuric acid; 2 millimoles (calculated as Br_2) of bromide-bromate solution ($r = 0.500$) was added. After further acidification and standing for half an hour, the precipitate was separated in a Gooch crucible, dried overnight at 50° and its weight found to be 0.2714 g. The filtrate was titrated, requiring 1.83 millimoles as Br_2, instead of 2.00 as the reaction would require. The deficiency was due to a slight precipitation of monobromo compound. This deficiency was checked by dissolving the first precipitate, after weighing, in methanol, acidifying and titrating with bromide-bromate solution, of which 0.19 millimole was required. This added to the other gives 2.02 instead of 2.00, but this discrepancy was within experimental error. It was assumed that 0.18 millimole or 0.0415 g. of monobromo compound had been precipitated. This should be subtracted from the weight of the first precipitate. The second precipitate weighed 0.3239 g., making a total of 0.5538 g. of dibromo compound. One and eighty-two hundredths millimoles of dibromo *p*-aminophenylacetic acid weighed 0.5621 g., showing a loss due to solubility of 0.0083 g. This was distributed as a correction between the two precipitates on the basis of the approximate volumes of filtrate, in this case equally. The first precipitate thus corrected was, therefore, $0.2714 - 0.0415 + 0.0041$ or 0.2340 g. This, divided by 0.6178 (the weight of two millimoles of product), gives 0.378, the rela-

tive yield, y, of dibromo compound corresponding to 0.500 for r, the relative amount of bromine added.

Frequently the first correction mentioned was unnecessary, because no incompletely brominated product was precipitated, as shown by the fact that the titration of the filtrate was theoretical. In other cases both corrections were much greater than in the illustration, making the results less accurate. If, as sometimes seemed to occur, a still lower brominated product, for example, monobromobenzylaniline (the highest being tribromo compound), was precipitated, it was nearly impossible to make the corrections and to obtain a reliable partial-bromination curve. In a few cases, where the partially brominated products were precipitated in large amounts, it was necessary to prevent this with a sufficient amount of methanol in solution, in order to obtain homogeneous reaction. The methanol was evaporated afterward, before filtration, at a low temperature, by a current of air.

Some compounds, for example, *m*-aminobenzene-sulfonic (metanilic) acid, give no precipitate at all. The curves for these were obtained indirectly by means of several competition experiments with a suitable competitor, using various amounts of bromide-bromate solution. That form of curve was assumed which was found, by trial, to make these competition experiments most consistent with one another. This was a very tedious process. The method was used also with *m*-aminobenzoic acid, which gives a precipitate, because the solubility of the latter is too great for a direct method. This was illustrated in the former paper.[7] Advantage was taken of the complete solubility of the product in dilute alkali. The method is inapplicable to compounds, such as benzylaniline, whose bromination products are not soluble in alkali. Those compounds to which the indirect method was applied are indicated in the table.

TABLE I

PARTIAL BROMINATIONS

(RELATIVE YIELD OF HIGHEST BROMINATED PRODUCT)

Ortho COMPOUNDS

Relative bromine added, r	0.075	0.100	0.200	0.250	0.333	0.400	0.500	0.667	0.750	0.833
Rel. yield, y. Calcd.	.008	.015	.052	.072	.109	.148	.222	.402	.525	.673
o-Bromo-aniline		.02	.059	.062			.231	.414	.519	
o-Chloro-aniline	.007	.020	.050	.073	.108	.152	.234		.55	
o-Toluidine				.073			.22	.37	.54	
Anthranilic acid	.010		.049	.075		.145	.223	.401	.537	.676
Methyl anthranilate							.214		.51	
Ethyl anthranilate				.06			.20		.52	
o-Nitro-aniline[b]							.004			
Ethyl-*o*-toluidine[a]			.06		.09					
2,5-Dichloro-aniline				.07			.22		.53	
2-Aminotoluene-4-sulfonic acid							.222		.51	
1,4-Xylidine-2[b]				.14	.19		.29			

[7] Ref. 3, p. 2223.

TABLE I (*Concluded*)

Meta COMPOUNDS

Relative bromine added, r	.200	.250	.333	.500	.600	.667	.750	.833
Rel. yield, z. Calcd	.046	.072	.126	.270	.370	.463	.577	.700
Aniline	.053	.075	.128	.270	.369	.469	.566	.693
m-Bromo-aniline				.270		.45		
m-Chloro-aniline		.06		.275		.468		
m-Toluidine	.06		.13	.270		.44		.72
m-Aminobenzoic acid[a]	.06			.275	.38	.45	.56	.72
Ethyl *m*-aminobenzoate				.269		.45		
m-Aminobenzene-sulfonic acid[a]	.06			.29	.39			
m-Nitro-aniline[b]						.018		
m-Nitromethylaniline[b]						.05		
m-Amino-acetanilide		.08		.25		.45	.56	
m-Aminophenol[b]	.15			.43				.80
m-Phenetidine		.08		.25			.55	

Para COMPOUNDS

Relative bromine added, r	.100	.250	.333	.500	.600	.667	.750	.833
Rel. yield y. Calcd	.028	.131	.205	.378	.490	.571	.675	.780
p-Bromo-aniline	.030	.136	.203	.376	.493	.566	.683	.774
p-Chloro-aniline	.026	.135	.207	.386		.569	.660	.776
p-Toluidine	.03	.14		.39			.69	
p-Iodo-aniline		.14		.39				
p-Aminobenzoic acid		.130	.203	.375	.489		.676	.781
Ethyl *p*-aminobenzoate		.125		.369				
p-Amino-acetophenone		.128	.212	.377		.572	.66	
p-Aminobenzyl cyanide				.40			.65	
p-Nitro-aniline[b]				.01				
p-Nitromethylaniline[b]				.04				
Sulfanilic acid[a]	.02	.13	.19	.38	.51		.70	
Arsanilic acid[b]			.10	.30			.52	
Ethyl-*p*-toluidine[a]	.03	.15		.35				
1,2-Xylidine-4		.15		.36			.68	
4-Aminotoluene-2-sulfonic acid[a]	.03	.16		.40	.48		.65	
p-Aminophenylacetic acid		.15		.378			.69	

m-DIAMINO COMPOUNDS

Relative bromine added, r	.200	.250	.333	.400	.500	.667	.750
Relative yield, y or z. Calcd	.200	.250	.333	.400	.500	.667	.750
m-Phenylenediamine, z	.20		.33		.50	.65	
2,4-Diaminotoluene,[a] y			.31	.41	.48		
2,4-Diaminochlorobenzene, y		.24			.49		.73

[a] Obtained indirectly. [b] Fails to follow relation.

The results of the partial-bromination experiments are summarized in Table I. "*Ortho* Compounds," includes those such as 2-aminotoluene-4-sulfonic acid, which would be expected to have the same curve. The same is true of "*Para* Compounds." The "calculated" values are those obtained from Equations 15, 2, 4 and 16, respectively. The experimental error is about 0.01 in those cases where three decimal places are given, and about 0.03 in the others.

Summary

The partial-bromination curves (yields of highest brominated product plotted against the relative amounts of bromine solution added) of 42 derivatives of aniline have been obtained. With the exception of nitro compounds (and three others), the curve depends only upon the type of

compound (*o*, *m* or *p*) and not at all upon the nature or directive influence of the other substituent. This means that the effect of that group upon rate of substitution is identical for the two or three positions substituted, that is, that directive influence is distributed symmetrically around the ring.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF TEXAS]

METHYLENE-CITRIC ANHYDRIDE THE ANILINE DERIVATIVES OF CITRIC AND ACONITIC ACIDS

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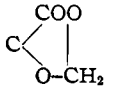
Introduction

We find that the anhydride of methylene-citric acid reacts with aniline to form a product which hydrolyzes with the elimination of the methylene group to the unsymmetrical anil of citric acid, known as citranilic acid. This observation would seem to indicate that methylene-citric anhydride, and consequently its acid are likewise of unsymmetrical structure. In our attempt to harmonize the accepted symmetrical formula assigned to methylene-citric acid with the formation of the unsymmetrical anil of citric acid we have proved beyond question that methylene-citric acid is of symmetrical structure and have developed an explanation of the mechanism of the apparently anomalous reaction of its anhydride with aniline. Furthermore, a method of preparation of methylene-citric anhydride has been discovered which makes this interesting substance readily available by the employment of a new process of making anhydrides.

Henneberg and Tollens[1] investigated the behavior of formaldehyde toward polybasic acids of the sugar group and found that the methylene radical could be introduced for two hydroxyl hydrogens, leaving the carboxyls intact. The condensing agent employed in this reaction is aqueous hydrochloric acid. Lobry de Bruyn[2] with co-workers investigated the action of formaldehyde on certain hydroxy acids in the absence of mineral acids, obtaining an entirely different result. They assume that formaldehyde and the hydroxy acid under this condition react with the elimination of water between the molecule CH_2O and the complex HO—C—COOH so as to produce methylene derivatives containing the group I; for example, formaldehyde with citric acid gives a methylene-citric acid to which Structure II is assigned.



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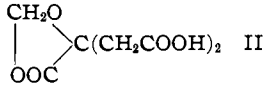

II

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[1] Henneberg and Tollens, *Ann.*, **292**, 31 (1896).

[2] Van Ekenstein and Lobry de Bruyn, *Rec. trav. chim.*, **19**, 178 (1900); **20**, 331 (1900).