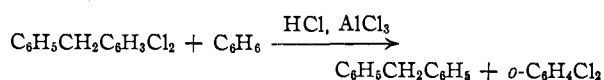


a transfer of a benzyl group from 3,4-dichlorodiphenylmethane to a benzene molecule.



The Hexamethylbenzene-Nitrobenzene-Aluminum Chloride Complex.—A colorless solution of 0.01 mole of hexamethylbenzene (m.p. 160–162°) in carbon disulfide was mixed with a light yellow solution of 0.01 mole each of nitrobenzene and aluminum chloride in the same solvent. A dark red color developed immediately. The solvent was removed under reduced pressure. There was ob-

tained a dark red-brown, almost black, crystalline solid. It reacted vigorously with water and was quite hygroscopic. It underwent gradual decomposition above 90–100°, but did not melt at temperatures above the m.p. of the 1:1 nitrobenzene-aluminum chloride complex. On hydrolysis, pure hexamethylbenzene could be recovered. Because of the characteristics of the material we did not attempt to prepare an analytical sample. The formation of a 1:1:1 complex was indicated by experiments on the variation of the color intensity as the composition was varied.

LAFAYETTE, INDIANA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

An Interpretation of Meta Orientation in the Alkylation of Toluene. The Relative Reactivity and Isomer Distribution in the Chloromethylation and Mercuration of Benzene and Toluene^{1,2}

BY HERBERT C. BROWN AND K. LEROI NELSON³

RECEIVED MARCH 11, 1953

The high proportions of meta isomers observed in the alkylation of monoalkylbenzenes under "non-isomerizing" conditions are not anomalous. A detailed examination of the available data on isomer distribution in the substitutions of toluene clearly demonstrates that there is no sharp division between reactions which give a high proportion of meta substitution and those which give little or no meta substitution. We propose that the importance of meta substitution is related to the "activity" of the attacking species and utilize the relative reactivity of toluene and benzene in the reaction under consideration as a measure of this "activity." A plot of the log of the relative toluene/benzene reactivities *vs.* the log of the toluene para/meta ratios indicates a simple linear relationship. Although some discrepancies appear, the data in these cases are open to question. As a crucial test of our proposal we undertook a reinvestigation of the chloromethylation reaction. We found that no chloromethylation of benzene occurs under the conditions for which a toluene/benzene ratio of 3 is reported. For reaction with trioxymethylene and hydrogen chloride in the presence of zinc chloride in glacial acetic acid at 60°, we observed a toluene/benzene ratio of 112 ± 12 with the distribution of isomers from toluene being 34.7, 1.3 and 64.0% ortho, meta and para, respectively. These results are in excellent agreement with our proposal. From the existing data on the distribution of isomers from the mercuration of toluene at 25° we predicted a value of 15–20 for the toluene/benzene ratio. We found a value of 30 ± 3. The yield of meta isomer, 12.3%, was somewhat higher than that previously reported.

Introduction

Orientations in Friedel-Crafts alkylations are frequently considered to be anomalous. Much of the early literature is confusing and misleading.^{4,5} However, it is now definitely established that alkylation of aromatics with aluminum chloride and alkyl halides leads to the formation of considerable quantities of the *m*-dialkyl isomer.^{6–8} Moreover, the exclusive formation of the meta isomer in the presence of molar quantities of the catalyst has been reported.⁹ Although the possibility of forming larger yields of the meta isomer than those given by the thermodynamic equilibrium value has been questioned,¹⁰ this result has been checked.¹¹ It was proposed¹¹ that the large yields of the meta isomer arise from isomerization¹² of the ortho and para

derivatives to the more stable¹³ σ -complexes¹⁴ formed by the meta dialkylbenzenes.

This explanation nicely accounts for the high yields of meta isomer obtained under isomerizing conditions. It does not account for the formation of large amounts of the meta isomer under conditions where isomerization is not an important reaction. For example, Condon⁸ has shown that no *o*- or *m*-cymene results when *p*-cymene is alkylated with propylene under mild conditions, yet under similar conditions all isomeric cymenes are obtained by the alkylation of toluene (Table I).

TABLE I

Temp., °C.	Catalyst	Isomer distribution		
		Ortho	Meta	Para
5	AlCl ₃ -MeNO ₂ or BF ₃ -Et ₂ O	37.5	29.8	32.7
65	AlCl ₃ -MeNO ₂ or BF ₃ -Et ₂ O	37.6	27.5	34.9

Numerous workers have proposed to account for the large yields of the meta isomer by "normal" alkylation to the 1,3,4-trialkyl derivative, followed by loss of the alkyl group in the 4-position.^{4,5} Condon's results effectively rule out this explanation.

We propose that the high yield of the meta isomer

(13) D. A. McCaulay and A. P. Lien, *THIS JOURNAL*, **73**, 2013 (1951).

(14) H. C. Brown and J. D. Brady, *ibid.*, **74**, 3570 (1952).

(1) The Catalytic Halides. X.

(2) Based upon a thesis presented by K. LeRoi Nelson in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) A.E.C. Fellow, 1950–1952.

(4) C. C. Price, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, Chapt. I.

(5) A. W. Francis, *Chem. Revs.*, **43**, 257 (1948).

(6) K. T. Serijan, H. F. Hipsher and L. C. Gibbons, *THIS JOURNAL*, **71**, 873 (1949).

(7) J. H. Simons and H. Hart, *ibid.*, **69**, 979 (1947).

(8) F. E. Condon, *ibid.*, **71**, 3544 (1949).

(9) J. F. Norris and D. Rubinstein, *ibid.*, **61**, 1163 (1939).

(10) K. S. Pitzer and D. W. Scott, *ibid.*, **65**, 803 (1943).

(11) D. A. McCaulay and A. P. Lien, *ibid.*, **74**, 6246 (1952).

(12) G. Baddeley, G. Holt and D. Voss, *J. Chem. Soc.*, 100 (1952).

in the isopropylation of toluene and similar mono-alkylbenzenes is the result of the high reactivity and resulting low selectivity of the isopropyl carbonium ion. Available data support the position that the relative yields of the meta isomer in substitutions involving toluene vary in a regular and predictable manner with the "activity" of the attacking agent. In a sense, then, the high yield of the meta isomer is not an anomalous property which is characteristic only of Friedel-Crafts substitutions.

Results and Discussion

Relationship between Activity and Meta Substitution.—A detailed examination of the available data on isomer distribution in the substitutions of toluene clearly demonstrates that there is no sharp division between reactions which give a high proportion of meta substitution and those which give little or no meta substitution. Thus, chlorination, chloromethylation and acylation are reported to give negligible amounts of the meta isomer, whereas mercuration and isopropylation result in the formation of relatively large amounts, with nitration and sulfonation giving intermediate values.

TABLE II
META SUBSTITUTION IN TOLUENE

Reaction	Conditions	m-Isomer	Lit. ref.
Acetylation	CH ₃ COCl + AlCl ₃	0	15
Bromination		0	16-18
Chlorination	Cl ₂ in HOAc at 24°	0.5	19
Chloromethylation		Small	20
Nitration	HNO ₃ in H ₂ SO ₄ at 30°	4.4	21, 22
	AcONO ₂ in Ac ₂ O at 0°	3.7	23
	AcONO ₂ in Ac ₂ O at 30°	4.4	23
Sulfonation	100% H ₂ SO ₄ at 35°	6.2	24
	SO ₃ (gas) at 40-55°	9	25
Methanesulfonylation	MeSO ₂ Cl + AlCl ₃ at 100°	15	26
Mercuration	Hg(ClO ₄) ₂ in aq. HClO ₄ at 25°	7	27
	Hg(ClO ₄) ₂ in aq. HClO ₄ at 85°	13	27
	Hg(OAc) ₂ at 110°	13	28, 29
	Hg(OAc) ₂ at 110°	21	27
Isopropylation	AlCl ₃ -MeNO ₂ or BF ₃ -Et ₂ O at 5°	29.8	8
	AlCl ₃ -MeNO ₂ or BF ₃ -Et ₂ O at 65°	27.5	8

(15) R. Pajean, *Bull. soc. chim.*, [5] **13**, 544 (1946).

(16) F. H. van der Laan, *Rec. trav. chim.*, **26**, 1 (1907).

(17) A. F. Holleman, *ibid.*, **33**, 183 (1914).

(18) J. B. Cohen and P. K. Dutt, *J. Chem. Soc.*, **105**, 501 (1914); *Proc. Chem. Soc.*, **30**, 15, 271 (1914).

(19) F. E. Condon, *THIS JOURNAL*, **70**, 1963 (1948). The per cent. meta is calculated from Condon's partial rate factors.

(20) P. Hill and W. F. Short, *J. Chem. Soc.*, 1123 (1935).

(21) A. F. Holleman, J. Vermeulen and W. J. DeMooy, *Rec. trav. chim.*, **33**, 1 (1914).

(22) W. W. Jones and M. Russell, *J. Chem. Soc.*, 921 (1947).

(23) C. K. Ingold, A. Lapworth, E. Rothstein and D. Ward, *ibid.*, 1959 (1931).

(24) A. F. Holleman and P. Caland, *Ber.*, **44**, 2504 (1911).

(25) K. Lauer and R. Oda, *J. prakt. Chem.*, **143**, 139 (1935).

(26) C. W. Vrieson, Ph.D. Thesis, Purdue University, 1952.

(27) W. J. Klapproth and F. H. Westheimer, *THIS JOURNAL*, **72**, 4461 (1950).

(28) S. Coffey, *J. Chem. Soc.*, **127**, 1029 (1925).

(29) A. J. Barduhn and K. A. Kobe, *Ind. Eng. Chem.*, **38**, 247 (1946).

A selection of the available data is reported in Table II.

We are proposing that the importance of meta substitution is related to the "activity" of the attacking species. As a convenient measure of this "activity" we utilize the relative reactivity of toluene and benzene toward the substitution reaction under consideration. According to this proposal, bromination involves a reaction of low activity—it is both highly selective between toluene and benzene (reactivity ratio of toluene/benzene = 467) and between the meta and para positions of toluene (no meta reported). Nitration involves an intermediate of moderate activity, the nitronium ion, NO₂⁺, and is only moderately selective between toluene and benzene (toluene/benzene = 23) and between the meta and para positions of toluene (4.4% meta). Finally, isopropylation involves a highly active intermediate, presumably the isopropyl carbonium ion, (CH₃)₂CH⁺, which gives only slight selectivity between the two aromatics (toluene/benzene = 2.1) and only slight selectivity between the meta and para positions (29% meta). The available experimental data are summarized in Table III.

A plot of the log of the relative toluene/benzene reactivities *versus* the log of the toluene para/meta ratios indicates a simple linear relationship between these quantities³⁰ (Fig. 1). There are, however, several serious discrepancies.

TABLE III
RELATIVE RATES OF SUBSTITUTION IN BENZENE AND TOLUENE

Reaction	Conditions	Reactivity ratio (k _{toluene} /k _{benzene})	Lit. ref.
Bromination	Br ₂ in HOAc with I ₂ at 25°	467	31
	Br ₂ in HOAc with I ₂ at 45°	272	31
Chlorination	Cl ₂ in HOAc at 24°	353	32
Nitration	AcONO ₂ in Ac ₂ O at 0°	27	23
	AcONO ₂ in Ac ₂ O at 30°	23	23
Acetylation	AcCl with AlCl ₃ at 0°	13.3	33
	AcCl with AlCl ₃ at 50°	8.4	34
Sulfonation	H ₂ SO ₄ in C ₆ H ₅ NO ₂ at 40°	5.1	35
Brosylation	<i>p</i> -BrC ₆ H ₄ SO ₂ Cl with AlCl ₃	3.7	36
Chloromethylation	CH ₂ O + HCl in HOAc at 85°	3.1	37
	CH ₂ OCH ₂ Cl in HOAc at 100°	2.9	38
Isopropylation	C ₃ H ₆ with AlCl ₃ in CH ₃ NO ₂ at 40°	2.1	39

(30) For convenience we shall hereafter refer to these quantities as the T/B and P/M ratios.

(31) E. Berliner and F. J. Bondhus, *THIS JOURNAL*, **68**, 2355 (1946); *ibid.*, **70**, 854 (1948).

(32) P. B. D. de la Mare and P. W. Robertson, *J. Chem. Soc.*, 279 (1943).

(33) Y. Ogata and R. Oda, *Bull. Inst. Phys. Chem. Research (Tokyo)*, **21**, 728 (1942).

(34) H. F. McDuffie, Jr., and G. Dougherty, *THIS JOURNAL*, **64**, 297 (1942).

(35) F. J. Stubbs, C. D. Williams and C. N. Hinshelwood, *J. Chem. Soc.*, 1065 (1948).

(36) S. C. J. Olivier, *Rec. trav. chim.*, **33**, 163 (1914).

(37) H. H. Szmant and J. Dudek, *THIS JOURNAL*, **71**, 3763 (1949).

(38) G. Vavon, J. Bolle and J. Calin, *Bull. soc. chim.*, [5] **6**, 1025 (1939).

(39) F. E. Condon, *THIS JOURNAL*, **70**, 2265 (1948).

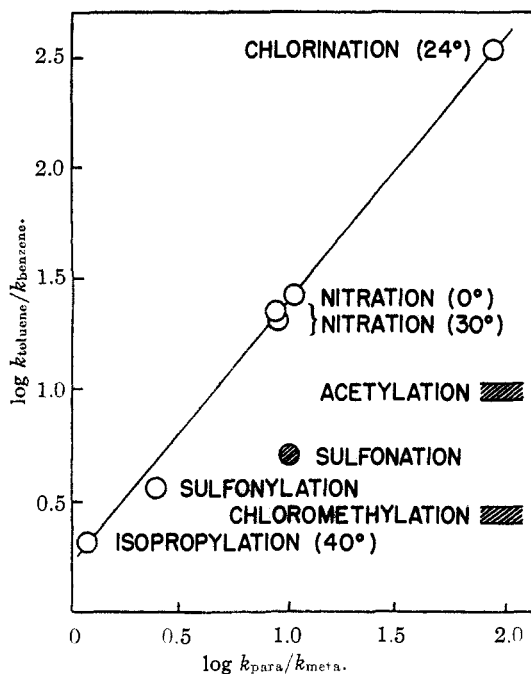


Fig. 1.—Relationship between the "activity" of the reagent and the degree of meta substitution. (The cross-hatched symbols represent data in serious disagreement with the generalization).

Sulfonation involves a T/B value of 5.1³⁵ and should give a P/M ratio of 2.5. Instead, a P/M ratio of 8.5 is reported.²⁴ However, it should be pointed out that the T/B is based on rate data obtained in nitrobenzene at 40° whereas the P/M ratio was obtained from the isomer distribution in sulfonation with 100% sulfuric acid at 35°. To be strictly comparable, the T/B and P/M ratios should be based on data from *identical* reaction conditions, since there is little doubt that the "activity" of the reagent must in part depend upon the reaction conditions. Moreover, Melander's observation⁴⁰ that hydrogen and tritium are replaced at different rates in sulfonation raises the possibility that the T/B ratio from kinetic studies may differ from the value that would be observed in a competitive experiment and therefore cannot be correlated with isomer distribution. The observable macroscopic kinetics of the substitution reaction may differ from the true kinetics of the substitution step so in order to use kinetic data as a source of T/B values it must be clear that the initial attack of the substituting reagent is rate determining.

Another discrepancy is offered by the acylation reaction. The T/B ratios of 8.4–13.3^{33,34} would, according to the theory, predict meta substitution of the order of 5%. Yet in the acetylation of toluene no significant formation of the meta isomer has been reported.¹⁵ Work designed to test this discrepancy is currently under way.⁴¹

A far more serious discrepancy is apparently offered by the data on chloromethylation. Here two different groups of investigators have reported T/B values of 2.9³⁶ and 3.1,³⁷ based upon kinetic data. According to the generalization here pro-

posed, such a low value would lead to the prediction of a large amount of the meta isomer in toluene. However, no author has reported the formation of the meta chloromethyl derivative in the reaction.

We therefore decided to test the validity of the proposed generalization by a careful re-examination of the T/B and P/M ratios for chloromethylation. Moreover, it is apparent from the data (Table II) that mercuration yields relatively large proportions of the meta isomer. We therefore predicted a T/B ratio of 15–20 for mercuration at 25°, and undertook a determination of this quantity as a further test of the generalization.

Chloromethylation.—The procedure of Grummitt and Buck⁴² involving a phosphoric acid-catalyzed reaction in acetic acid gave less than 10% of benzyl chloride after 22 hours at 75°. Darzens⁴³ has suggested that chloromethyl acetate was the actual chloromethylating agent in acetic acid. However, reactions with this reagent at 75–80° for 16 hours without added catalyst and at 60° for 4 hours with added zinc chloride failed to yield any benzyl chloride. (Subsequent results with *s*-dichloromethyl ether suggest that chloromethyl acetate would be successful for reaction times of the order of 100 hours.)

These results as well as a yield of less than 10% for the reaction between benzene, trioxymethylene and hydrogen chloride at 60° and 4 hours in the presence of added zinc chloride led us to question the reports of rapid uncatalyzed reactions^{37,38} which had been used for the kinetic determination of reactivity ratios. Thus the kinetic data³⁷ indicated that the uncatalyzed reaction between trioxymethylene, hydrochloric acid and benzene in glacial acetic acid was 10% complete in 10 minutes. We therefore undertook the chloromethylation of benzene under the exact conditions used by Szmant and Dudek³⁷ with the exception that all materials were increased fivefold to permit isolation of the products and the reaction was carried out for 24 hours. We were unable to isolate any benzyl chloride—there was no evidence of any substitution of the aromatic.⁴⁴

The optimum conditions which we developed for the chloromethylation of benzene involved the reaction of 3 moles of benzene, 2 equivalents of trioxymethylene and 30 g. of zinc chloride in 200 ml. of glacial acetic acid with excess anhydrous hydrogen chloride (passed in to saturation during the first 3 hours) at 60° for 72 hours. The yield of benzyl chloride is 65%, based on formaldehyde. Toluene was much more reactive—a 57% yield of the product was obtained in only 18 hours with half the quantity of the zinc chloride catalyst. In ease of manipulation and quality of product the procedure proved quite advantageous over that described by Blanc.⁴⁵

Competitive experiments between toluene and

(42) O. Grummitt and A. Buck, *Org. Syntheses*, **24**, 30 (1944).

(43) G. Darzens, *Compt. rend.*, **208**, 818 (1939).

(44) The analytical procedure used in the kinetic studies^{37,38} requires the almost instantaneous hydrolysis of the chloromethyl ethers which are present in the reaction mixtures. We have observed that the hydrolysis of *s*-dichloromethyl ether occurs at a rapid, but certainly not instantaneous, rate even in the presence of dilute alkali.

(45) G. Blanc, *Am. Perfumer*, **17**, 841 (1923); *Perfumery Essent. Oil Record*, **14**, 40 (1929).

(40) L. Melander, *Arkiv. Kemi*, **3**, 213 (1950).

(41) Work in progress with Mr. H. L. Young.

TABLE IV
 ISOMER DISTRIBUTION AND PARTIAL RATE FACTORS

Reaction	Conditions	Isomer distribution			T/B	Partial rate factors ^a			P/M	Ref.
		Ortho	Meta	Para		<i>o</i> / <i>t</i>	<i>m</i> / <i>t</i>	<i>p</i> / <i>t</i>		
Chlorination	Cl ₂ in HOAc at 24°	57.7 ^b	0.5 ^b	41.8 ^b	353	611	5.30	887	167.3	19, 32
Chloromethylation	CH ₃ O in HOAc at 60° with HCl and ZnCl ₂	34.7	1.3	64.0	112	117	4.37	430	98.4	Present study
Nitration	A, AcONO ₂ in Ac ₂ O at 0°	58.1	3.7	38.2	27	47.1	3.00	61.8	20.6	23
	B, AcONO ₂ in Ac ₂ O at 30°	58.4	4.4	37.2	23	40.3	3.04	51.4	16.9	23
	C, HNO ₃ in CH ₃ NO ₂ at 30°	58.5	4.4	37.1	21	36.8	2.77	46.7	16.9	23
Mercuration	A, Hg(OAc) ₂ in HOAc at 30° with HClO ₄	17	6	77	30 ^c	15.3	5.40	139	25.7	27
	B, Same as above	20.6	12.3	67.1	30	18.6	11.1	121	10.9	Present study
Sulfonation	100% H ₂ SO ₄ at 35°	31.8	6.2	62.0	5.2 ^d	4.96	0.97	19.4	19.9	24, 35
Sulfonylation	A, MeSO ₂ Cl with AlCl ₃ at 100°	49	15	36		5.44 ^e	1.67 ^e	7.99 ^e	4.80	26
	B, <i>p</i> -BrC ₆ H ₄ SO ₂ Cl with AlCl ₃				3.7					36
Isopropylation	C ₃ H ₈ at 40° with AlCl ₃	37.6 ^f	28.5 ^f	33.9 ^f	2.1 ^g	2.37	1.80	4.27	2.37	8, 39

^a Partial rate factors = 120 (% observed/% for statistical) ($k_{\text{toluene}}/k_{\text{benzene}}$). ^b Estimated from Condon's partial rate factors (see ref. 19). ^c From present study. ^d Interpolated from rate data at 25 and 40° in nitrobenzene solution. Note that conditions differ from those used for isomer distribution. ^e Estimated with T/B value for brosylation. ^f Interpolated from data at 5 and 65°. ^g In nitromethane as solvent.

benzene under similar conditions were carried out and the relative reactivities determined by recovery and separation of the unreacted hydrocarbons. The T/B ratio was indicated to be in the neighborhood of 25, much higher than the value based on the kinetic data.^{37,38} However, the quantitative isolation of small amounts of toluene in the presence of large amounts of benzene (and chloromethyl derivatives) offered difficulty and the calculated T/B ratio varied considerably from experiment to experiment. We therefore decided to base our analysis on the separation of the chloromethyl derivatives, conversion to the corresponding hydrocarbons (toluene and the xylenes) by reduction with lithium aluminum hydride, followed by analysis by ultraviolet absorption.⁴⁶

The results showed that the meta isomer is formed only to the extent of approximately 1%. Moreover, in contrast to the reported T/B ratios of 2.9³⁸–3.1,³⁷ we obtained a value of 112 ± 12. These values are in excellent agreement with the proposed relationship (Fig. 1).

Mercuration.—The mercuration of a mixture of benzene and toluene was carried out in glacial acetic acid with added perchloric acid as catalyst.²⁷ Initially we attempted to convert the product into the corresponding arylmercuric chloride, followed by hydrolysis to the hydrocarbons (benzene and toluene), from which the T/B ratio could be obtained. However, after 18 hours in refluxing hydrochloric acid the yield of hydrocarbon was negligible.⁴⁷

We then carried out the analysis by converting the arylmercuric bromides into the aryl bromides by reaction with bromine. Usually the bromination is carried out in chloroform, but this solvent absorbs strongly in the 12–15 micron region. Bromination of the mixed arylmercuric bromides in carbon disulfide gave a mixture of bromobenzene and the isomeric bromotoluenes in a solvent suitable directly for analysis by infrared absorption.

The analysis⁴⁶ indicates a T/B ratio of 30 ± 3 with 12.3% of the meta isomer. The T/B ratio

(46) We are indebted to Dr. C. F. Glick of the Physical Research Laboratory of the Barrett Division for assistance with the analysis.

(47) Private communication from Dr. Saul Winstein later revealed the facile and quantitative reduction of organomercury compounds with lithium aluminum hydride.

is of the magnitude to be expected for the 7% meta isomer reported by Klapproth and Westheimer.²⁷ We are, however, unable to account for the difference between the two values for the meta isomer. Different analytical procedures were utilized in the two studies. A careful re-examination of the validity of these procedures appears necessary. We hope to resolve the discrepancy by further investigation. However, within the relatively large limits of error set by the discrepancy in the two values for the meta isomer, it is apparent that the T/B and P/M ratios correspond in magnitude to the proposed generalization.

Theoretical Implications.—It is now generally recognized that substitution in the ortho position is complicated by steric factors.^{48,49} For this reason the polar effect of a substituent is best evaluated in terms of the para/meta ratio rather than in terms of ratios involving the ortho position.⁴⁸ It is apparent that the varying steric requirements of the attacking agents could markedly affect the T/B ratio, while the P/M ratio would be independent of this effect. In order to eliminate such complications, it appeared desirable to calculate the partial rate factors for substitution and to compare the log of the partial rate factor for the para position of toluene with the log of the ratio of the partial rate factors for the para and meta positions of toluene. The data are summarized in Table IV and represented graphically in Fig. 2. The figure reveals a simple linear relationship with only our value for large meta substitution in mercuration and the value for sulfonation (based upon experiments under different conditions) showing serious deviations.

Thus far we have discussed the correlation of the "activity" of the substituting reagent with the observed isomer distribution and molecular selectivity only as an empirical generalization. However, it is apparent that even as an empirical relationship, the generalization should be very useful. For example, it indicated an apparent inconsistency in the published data for the chloromethylation reaction—an inconsistency which has now been resolved. Moreover, it permits one to predict

(48) K. L. Nelson and H. C. Brown, *This Journal*, **78**, 5605 (1951).

(49) L. N. Ferguson, *Chem. Revs.*, **86**, 47 (1952).

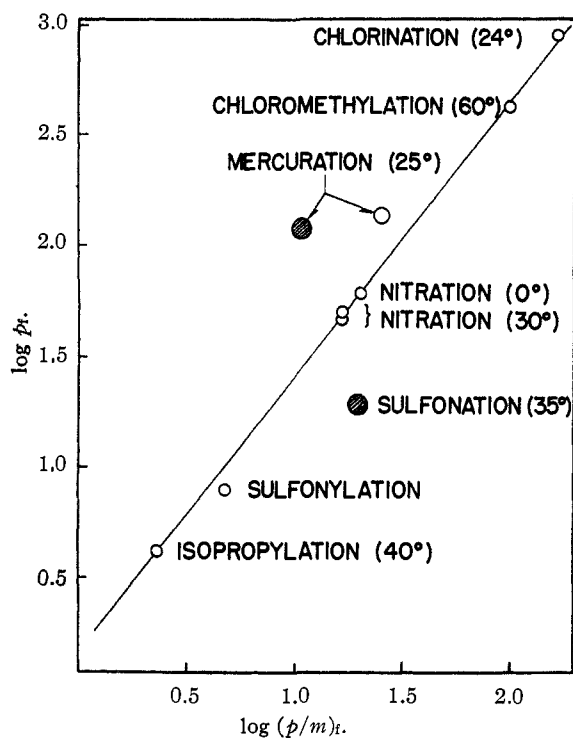


Fig. 2.—Relationship between the "activity" of the reagent and the degree of meta substitution, in terms of the partial rate factors.

that the amount of meta substitution in the chlorination and bromination of toluene will both be small, with the amount of meta substitution in bromination somewhat less than in chlorination. Further, it suggests that either the published data on the relative reactivity of benzene and toluene in acylation are erroneous, or significant quantities of the meta isomer must be formed. We are testing certain of these predictions.

It is reasonable to correlate the "activity" of the attacking agent with its electrophilic properties. Certainly the electrophilic character of bromine, nitronium ion and isopropyl carbonium ion would be expected to increase in the order listed. This is also the order we have found for the reactivity of these reagents: $\text{Br}_2 < \text{NO}_2^+ < (\text{CH}_3)_2\text{CH}^+$. We may therefore predict that the electrophilic character or "activity" of the following carbonium ions will increase in the order: $\text{RCO}^+ < (\text{CH}_3)_3\text{C}^+ < (\text{CH}_3)_2\text{CH}^+ < \text{CH}_3\text{CH}_2^+ < (\text{CH}_3)^+$.⁵⁰

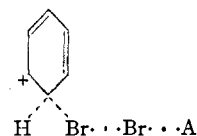
Thus in Friedel-Crafts acylations we would expect relatively small amounts of the meta isomer. This is, of course, in agreement with the facts so far as they are established. Moreover, we may predict that ethylation should result in the formation of a larger quantity of the meta isomer than in the isopropylation of the corresponding monoalkylbenzene. Indeed, we should expect an approach to a statistical distribution (1 para/2 meta). On the other hand, *t*-butylation should be more selective than isopropylation and we should correspondingly expect to find a smaller quantity of the

(50) We wish to emphasize that at the present time we are unaware of any evidence which requires the formation and reaction of methylcarbonium ions in Friedel-Crafts reactions. See H. C. Brown and M. Grayson, *THIS JOURNAL*, **75**, 6285 (1953).

meta isomer (strictly speaking we should make predictions only with regard to the para/meta ratios).

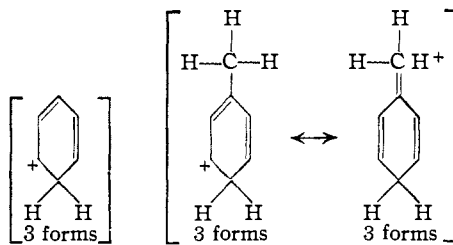
Recently Hennion and his co-workers⁵¹ reported an interesting study of the isomer distribution in the *t*-butylation of isopropylbenzene as contrasted with that obtained in the isopropylation of *t*-butylbenzene. They noted that the isopropylation reaction formed much larger amounts of the meta isomer than were obtained in the *t*-butylation reaction. They proposed to account for this result in terms of steric effects operating from the meta positions in the transition state. However, it is apparent that the results are entirely explicable, without additional hypotheses, in terms of the theory outlined in this paper. The P/M ratio of 10 for *t*-butylation, estimated from their data, is of the magnitude to be expected, while the corresponding ratio for isopropylation is in the neighborhood of 2.^{51a}

In aromatic bromination it appears that the transition state involves the aromatic molecule, a bromine molecule, and some additional electrophilic agent (A), which may be an additional bromine molecule.⁵² It may be predicted that a detailed



study of the bromination reaction would show a regular decrease in the T/B ratio with a corresponding decrease in the P/M value as the bromination catalyst is altered from the relatively mild electrophilic agent, iodine, to the more strongly acidic materials, $\text{SnBr}_4 < \text{FeBr}_3 < \text{AlBr}_3$. In this connection it has been noted that significant amounts of the meta isomer are formed in the iron-catalyzed bromination of toluene.⁵³

It is now appropriate to examine the physical basis for the proposed generalization. It has been pointed out in an earlier paper of this group that toluene forms much more stable σ -complexes than



(51) G. F. Hennion, A. J. Driesch and P. L. Dee, *J. Org. Chem.*, **17**, 1102 (1952).

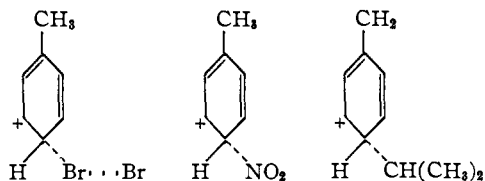
(51a) ADDED TO PROOF.—M. J. Schlatter and R. D. Clark [*THIS JOURNAL*, **75**, 361 (1953)], have recently reported the results of a careful study of the isomer distribution in the *t*-butylation of toluene. Under non-isomerizing conditions there is formed 7% of meta *t*-butyltoluene and 93% of the para isomer. This result (P/M = 13) verifies the conclusion that *t*-butylation, involving as it does a relatively stable carbonium ion, should result in the formation of much smaller amounts of the meta isomer than are observed in substitutions involving the more active species, isopropyl carbonium ion.

(52) P. W. Robertson, J. E. Allan, K. N. Haldane and M. G. Simmers, *J. Chem. Soc.*, 933 (1949); P. W. Robertson, P. B. de la Mare and W. T. G. Johnston, *ibid.*, 276 (1943).

(53) Private communication from Professor C. C. Price and Mr. T. G. Kane, Notre Dame University. Unfortunately the T/B ratio under the same reaction conditions has not been determined.

does benzene.⁵⁴ This is attributed to powerful hyperconjugative interaction at the demand of the electron deficient center.

A reagent such as bromine which is a relatively stable entity, only weakly electrophilic, will require a high contribution of electrons from the aromatic ring in the transition state. The more electrophilic nitronium ion will require a somewhat lesser contribution, while the highly electrophilic isopropyl carbonium ion will require the least contribution. In other words the transition states involving these three intermediates will require a higher electron density in the partially formed carbon-bromine bond, with decreasing electron densities in the partially formed carbon-nitrogen and carbon-carbon bonds. The greater the required electron density in the partially formed new bond in the transition state, the more important will be the contribution of electrons from the methyl group. Thus a methyl group will have



a large effect on the reactivity of the aromatic ring in bromination, a smaller effect in nitration and a still smaller effect in alkylation.

There have been a number of attempts to account for the isomer distribution in aromatic substitution by estimating the relative electron density at individual positions of the aromatic rings^{55,56} or the index of free valency,⁵⁷ or the relative stability of an idealized transition state or carbonium ion intermediate.⁵⁸⁻⁶¹ These treatments have largely ignored the nature of the substituting agent in affecting the isomer distribution. It follows that such treatments must be considered in the nature of first approximations and cannot form the basis of a fully satisfactory theoretical approach to orientation problems until they incorporate within the theory the effect of the structure of the substituting agent.

In the present paper we have restricted our discussion to toluene and similar monoalkylbenzenes. However, it must be apparent that the treatment should be applicable to all monosubstituted aromatics. Various monosubstituted aromatics should give lines which run more or less parallel to that for toluene. If the substituent is of the class known as meta-directing, the line will lie in a region where $\log p_t$ and $\log (p/m)_t$ have negative⁶² values (Fig. 3). A special problem is posed for derivatives

(54) H. C. Brown and W. J. Wallace, *THIS JOURNAL*, **75**, 6268 (1953).

(55) T. Ri and H. Eyring, *J. Chem. Phys.*, **8**, 433 (1940).

(56) C. C. Price, *Chem. Revs.*, **29**, 37 (1941).

(57) R. Daudel and A. Pullman, *J. chim. phys.*, **43**, 77 (1946).

(58) G. W. Wheland, *THIS JOURNAL*, **64**, 900 (1942).

(59) C. C. Price, *ibid.*, **75**, 5833 (1951).

(60) M. J. S. Dewar, *ibid.*, **74**, 3357 (1952).

(61) J. D. Roberts and A. Streitwieser, Jr., *ibid.*, **74**, 4723 (1952).

(62) This line will extend to positive values for free radical substitutions [R. L. Dannley and E. C. Gregg, Jr., *Abstracts of Papers, 121st Meeting of the American Chemical Society, Buffalo, N. Y., March, 1952, p. 1K*].

where the substituent is a halogen. Here it is noted that the partial rate factor for para substitution is greater than one for halogenation and less than one for nitration. However, this anomaly is easily resolved. It is apparent from Fig. 3 that it is possible for $\log p_t$ to have positive values for reactions of high "activity" (high values of $\log (p/m)_t$) and negative values for reactions of low "activity." Unfortunately, the data available at the present time are too meager to permit a satisfactory test of the extended theory.

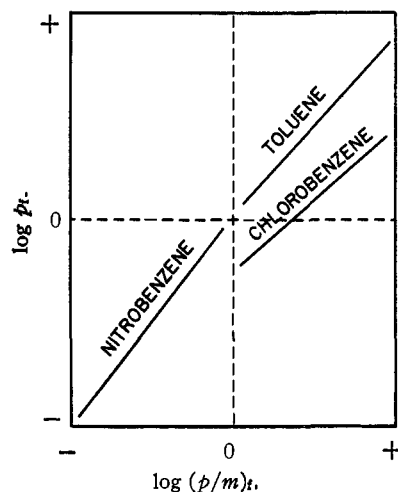


Fig. 3.—Diagram illustrating the proposed extended treatment for three different types of monosubstituted benzenes.

Experimental Part

Effect of Conditions in Chloromethylation of Benzene and Toluene.—In order that other investigators may not needlessly attempt reactions which we know to fail and also in order to assist them in establishing desirable conditions for reactions with other compounds we are briefly tabulating the results of our investigations (Table V). It is apparent from the tabulated results that the occurrence of secondary condensation to give diphenylmethane derivatives is greatly influenced by both the substituent and the amount of catalyst that is used. The large difference in reactivity between benzene and toluene suggests that little, if any, catalyst would be required for very reactive aromatic compounds. It is believed that the optimum procedure for any aromatic derivative should emphasize the use of the minimum amount of catalyst necessary to give reaction in a tolerable length of time.

Attempted Uncatalyzed Chloromethylation of Benzene.—Reaction conditions were identical with those used by Szmant and Dudek³⁷ for the determination of relative chloromethylation rates. In a 1-liter 4-necked round-bottomed flask equipped with a sealed stirrer, reflux condenser and addition funnel were placed 16.5 g. (0.183 mole) of trioxymethylene (Eastman Kodak Co.), 625 ml. of glacial acetic acid and 39.0 g. (0.50 mole) of benzene (Barrett, thiophene-free). The mixture was heated to 85° and stirred while 55 ml. (0.56 mole) of concentrated hydrochloric acid was added. The reaction mixture was maintained at 85° and stirred for 24 hours, cooled and poured over 300 g. of crushed ice. The layers were separated and the aqueous acetic acid layer extracted with two portions of petroleum ether (35-37°) which had been used to rinse the reaction vessel. The combined organic material was washed with 500 ml. of cold 10% potassium carbonate solution by judicious shaking until the evolution of carbon dioxide (from hydrolysis of the unreacted *s*-dichloromethyl ether) ceased. The solution was dried over a mixture of calcium chloride and potassium carbonate and the petroleum ether and unreacted benzene removed by simple distillation. The vapor temperature did not increase above 80° until a residue of only 1.8 g. remained in the flask. The refractive index of this residue (n_D^{20})

TABLE V
 EFFECT OF CONDITIONS IN CHLOROMETHYLATION OF BENZENE AND TOLUENE

Aromatic, moles	CH ₂ O, moles	HCl	HOAc, ml.	Catalyst	Temp., °C.	Time, hr.	Yield, %	By-product	Cf. ref.
3 C ₆ H ₆	1.5	150 ml. concd.	300	150 ml. H ₃ PO ₄	75	22	<10	DCME ^b	43
2 C ₆ H ₆	1	(1.45 moles AcCl)	200	(50 ml. Ac ₂ O)	75-80	16	0	CMA ^c	44
2 C ₆ H ₆	1.45	gas to saturation + (1.45 moles AcCl)	200	20 g. ZnCl ₂ + (10 ml. Ac ₂ O)	60	4	0	CMA ^c	
0.5 C ₆ H ₆	0.55	55 ml. concd.	625		85	24	0	DCME ^b	38
8 C ₆ H ₆	2	2 hr. ^a		60 g. ZnCl ₂	60	3	42	DCME ^b + 30% DAM ^d	
8 C ₆ H ₆	2	1 hr. ^a		30 g. ZnCl ₂	60	1	<10	DCME ^b	
3 C ₆ H ₆	2	4 hr. ^a	400	40 g. ZnCl ₂	60	4	<10	DCME ^b	
2 C ₆ H ₆	1	8 hr. ^a	150	21.3 g. ZnCl ₂	60	9	18	DCME ^b + 9% DAM ^d	
3 C ₆ H ₆	2	3.5 hr. ^a	200	30 g. ZnCl ₂	60	72	65	DCME ^b + 5% DAM ^d	
2.2 C ₆ H ₅ Me	2	3 hr. ^a	200	30 g. ZnCl ₂	60	25	66	DCME ^b + 16.5% DAM ^d	
2.2 C ₆ H ₅ Me	2	3 hr. ^a	200	30 g. ZnCl ₂	60	6	60	DCME ^b + 10% DAM ^d	
2 C ₆ H ₅ Me	2	3 hr. ^a	300	15 g. ZnCl ₂	60	6	29	DCME ^b + ca. 0% DAM ^d	
2 C ₆ H ₅ Me + 2 C ₆ H ₆	2	3 hr. ^a	200	15 g. ZnCl ₂	60	18	57	DCME ^b + ca. 0% DAM ^d	

^a Time required to saturate mixture with anhydrous hydrogen chloride gas. ^b DCME = *s*-dichloromethyl ether. ^c CMA = chloromethyl acetate. ^d DAM = diarylmethane.

1.4762) indicated that it could not have contained more than a trace amount of benzyl chloride.

Competitive Catalyzed Chloromethylation of Benzene and Toluene.—The apparatus consisted of a 1-liter 4-necked round-bottomed flask equipped with a sealed stirrer, reflux condenser attached to a water cascade scrubber to remove effluent hydrogen chloride gas, a thermometer to measure the temperature of the reaction mixture and a medium porosity fritted glass filter stick to disperse the gaseous hydrogen chloride as it was introduced below the liquid surface. The hydrogen chloride was prepared by dehydration of concentrated hydrochloric acid with concentrated sulfuric acid. The system was gas tight and equipped with appropriately arranged traps and sulfuric acid bubblers to assist in regulating the flow of gaseous hydrogen chloride. In the reaction flask were placed 60.0 g. (0.67 mole) of trioxymethylene (Eastman Kodak Co.), 15.0 g. of zinc chloride (Mallinckrodt), 200 ml. of glacial acetic acid, 156.2 g. (2 moles) of benzene (Barrett, thiophene-free, rectified) and 184.3 g. (2 moles) of toluene (Baker, C.P., rectified). The mixture was stirred and heated at 60° while anhydrous hydrogen chloride (from approximately 200 ml. of concentrated hydrochloric acid) was bubbled in over a period of 3 hours. The heating mantle was raised or lowered as required to compensate for the heat effect which at its peak is sufficient to maintain the reaction temperature without external heating. After 3 hours the absorption of hydrogen chloride and the heat effect had largely subsided. The stream of hydrogen chloride was reduced to a mere trickle and stirring and heating continued for a total reaction time of 18 hours.

The reaction mixture was quickly cooled to 15° and poured over 250 g. of crushed ice in a 1-liter separatory funnel. The system was thoroughly agitated and as soon as the ice had melted, the lower aqueous layer was drained. The organic layer was underlaid with 500 ml. of cold 10% potassium carbonate solution and judiciously agitated until the evolution of carbon dioxide had essentially ceased. The aqueous acid and carbonate layers were combined and extracted with petroleum ether (35-37°) which had been used to rinse the reaction apparatus. The combined organic material was dried over a mixture of calcium chloride and anhydrous potassium carbonate. Rectification, first at atmospheric pressure to remove the petroleum ether and unreacted benzene and then at 95 mm. to remove the toluene, left a residue of 159.0 g. of product (*n*_D²⁰ 1.5353). A small intermediate fraction was estimated (by comparison of ultraviolet spectra) to contain approximately 0.3 g. of benzyl chloride.

A 50.0-g. portion of this chloromethylation product was reduced with 7.2 g. (0.19 mole) of lithium aluminum hydride in 85 g. of freshly purified tetrahydrofuran at 65° for 48 hours. The excess lithium aluminum hydride was decomposed by the cautious addition of water and the mixture was then poured over ice and sulfuric acid. The layers were separated and the aqueous phase extracted with petroleum ether (35-37°) that had been used to rinse the apparatus. The organic material was washed with 250 ml. of 10% potassium carbonate solution and dried over calcium chloride. The material was rectified using added phenetole as a chaser (the phenetole had been shown not to azeotrope with a mixture of toluene and the three xylenes). A significant por-

tion of the material (approximately 15 ml.) distilled at 116-117° and was identified by means of its infrared spectrum as *n*-butyl alcohol. Both the phenetole and the *n*-butyl alcohol were found to complicate the ultimate analysis of the product. The combined distillate was extracted with 85% phosphoric acid, azeotropically distilled with *n*-butyric acid through a miniature Podbielniak column (8 mm. × 24", Heligrad Hastelloy packing) and again extracted with phosphoric acid and then dried over a mixture of calcium chloride and anhydrous potassium carbonate. The infrared and mass spectra taken before and after these treatments indicated that no measurable alteration had occurred in the distribution of the principal products.

A precise quantitative analysis of the final mixture (25.3 g.) of toluene and xylenes was carried out by means of ultraviolet absorption.⁴⁶ From the results of duplicate determinations and a check analysis of a known mixture of similar composition the analysis with indicated absolute limits of accuracy was reported as: toluene, 0.8 ± 0.5; *o*-xylene, 34.1 ± 1.0; *m*-xylene, 1.3 ± 0.5; *p*-xylene, 62.9 ± 0.5. This represents an over-all yield on reduction and isolation of 64%. On this basis the 159.0 g. of chloromethylation product would have been converted into 80.7 g. of the hydrocarbon mixture. Adding 0.2 g. as a correction for the benzyl chloride lost in the forerun, this hydrocarbon represents a yield of 0.755 mole of xylenes and 0.0092 mole of toluene. From the competitive rate expression of Ingold,²³ averaging the toluene/benzene ratio for 64% reduction with that estimated for 100% reduction, and allowing a 10% error in the results

$$k_{\text{C}_6\text{H}_5\text{Me}}/k_{\text{C}_6\text{H}_6} = 112 \pm 12$$

$$k_{\text{para}}/k_{\text{meta}} = 49 \pm 5$$

Competitive Mercuration of Benzene and Toluene.—The procedure was similar to that of Klapproth and Westheimer.²⁷ In a 1-liter 4-necked round-bottomed flask equipped with sealed stirrer, condenser and thermometer were placed 31.9 g. (0.10 mole) of mercuric acetate (Baker, C.P.), 200 ml. of glacial acetic acid, 78.1 g. (1.0 mole) of benzene (Barrett, thiophene-free, rectified) and 18.4 g. (0.2 mole) of toluene (Baker, C.P., rectified). To this mixture at 25° was added 10 ml. of 60% perchloric acid (Mallinckrodt, A.R.) in 100 ml. of glacial acetic acid. The mixture was stirred at 25° for 6.5 hours. The reaction was stopped by dilution with 400 ml. of water. The unreacted aromatic hydrocarbons were removed by aspiration. To the resulting solution was added 20.6 g. (0.2 mole) of sodium bromide (Mallinckrodt, A.R.) in 100 ml. of water. The precipitate was filtered and washed on the filter with two 100-ml. portions of dilute sodium bromide solution. The product was dried to constant weight in a vacuum desiccator. The mixture of crude arylmercuric bromides was slurried with approximately 200 ml. of carbon disulfide, chilled and treated with 16 g. (0.1 mole) of bromine (Mallinckrodt) in small portions. After standing for several hours, the mixture was washed with dilute sodium bisulfite solution followed by dilute sodium bromide solution. The carbon disulfide solution was dried over calcium chloride and filtered.

A precise quantitative analysis of the mixture of aryl bromides in carbon disulfide solution (235 g.) was carried

out by means of infrared absorption.^{4b} From the results of duplicate determinations and a check analysis of a known mixture of similar composition the analysis with indicated absolute limits of accuracy was reported as: bromobenzene, 17.9 ± 1.0 ; *o*-bromotoluene, 16.9 ± 0.5 ; *m*-bromotoluene, 10.1 ± 0.5 ; *p*-bromotoluene, 55.1 ± 0.5 . This represents an over-all yield of 41% (based on mercuric acetate). From the competitive rate expression of Ingold,²³ averaging

the toluene/benzene ratio for 41% conversion with that estimated for 100% conversion and allowing a 10% error in the results

$$k_{\text{C}_6\text{H}_4\text{Me}}/k_{\text{C}_6\text{H}_6} = 30 \pm 3$$

$$k_{\text{para}}/k_{\text{meta}} = 5.5 \pm 0.6$$

LAFAYETTE, IND.

NOTES

Ion-exchange Chromatography of the Products of the Non-enzymatic Sugar Amino Acid Reaction, and the Occurrence of the Reaction in Liver Extracts

BY A. ABRAMS AND H. BORSOOK

RECEIVED JULY 27, 1953

The non-enzymatic condensations of reducing sugars with amino acids, first investigated by Maillard,¹ and often referred to as the browning reaction, have recently been reviewed.^{2,3} Despite the many years that these reactions have been under investigation, the nature of the products has remained uncertain mainly because of the inadequacies of the available analytical methods. Recently the methods of paper chromatography have been applied to the problem⁴⁻⁶ with considerable success but the use of ion-exchange chromatography does not seem to have been reported.

Using ion-exchange chromatography and carboxyl-C¹⁴-L-leucine we have been able to resolve some of the products formed when the amino acid reacts with D-glucose and with D-ribose. A non-enzymatic reaction with glucose also was observed to take place when leucine was added to liver homogenates, the reaction having been brought about under conditions typical for browning reactions in natural systems. The sugar amino acid reaction in concentrated liver extracts was reported some years ago by Agren.^{7,8}

Only one radioactive product was detected when the glucose and leucine reacted, and no visible browning took place. Paper chromatographic evidence made it probable that it was the simple glycosyl amino acid (or Schiff base) which is generally considered to be the initial product formed in the browning reaction although direct evidence is lacking.³

The reaction between ribose and leucine carried out under approximately the same conditions as for glucose resulted in the formation of a number of radioactive products and considerable brown color. It should be noted that only those products which

retain the carboxyl group of the leucine have been detected. These products must represent those formed in the initial stages of the reaction since the later stages involve the loss of the carboxyl group as CO₂.⁹

These findings need to be taken into account in interpreting metabolic findings with amino acids, especially radioactive amino acids. It has already been pointed out that amino acids and glucose in the same mixture may cause a considerable error in the determination of glucosamine with Ehrlich's reagent.^{10,11} It is of interest to note also that the stimulation of the growth of certain bacteria by heated culture media, has been ascribed to the products of the Maillard reaction.¹²

Materials and Methods.—Ion-exchange chromatography was carried out on Dowex-50 cation resin (250-500 mesh) in conjunction with an automatic fraction collector, eluting with various strengths of hydrochloric acid according to the directions of Moore and Stein,¹³ except that the column was kept at 4° by the use of a jacketed column, through which cold water was allowed to circulate.¹⁴

The radioactivity of each fraction was determined by means of a Geiger-Müller end window counter on 0.2-ml. aliquots dried on Tygon painted aluminum cups¹⁴ or copper cups.

The leucine was C¹⁴-carboxyl labeled and had a specific activity of 26500 c.p.m./mg.¹⁵

Experimental and Results

The Reaction in Liver Extracts.—A typical experiment leading to the formation of a glucose-leucine compound follows. A guinea pig liver, 10 g. wet weight, was homogenized in 40 ml. of a salt mixture¹⁶ at pH 7.4 to which 5.24 mg. of radioactive leucine had been added. The homogenate was incubated for 3 hours at 37°, and the proteins were removed by heating at 100° at pH 5, and the soluble extract was brought to dryness by evacuation in a rotary dryer at a temperature of about 60-80°. The residue was taken up in 5 ml. of 1.5 N hydrochloric acid and subjected to ion-exchange analysis as described under Methods. The results are shown in Fig. 1. It can be seen that a major radioactive component was resolved as a fairly

(9) F. H. Stadtman, C. O. Chichester and G. Mackinney, *This Journal*, **74**, 3194 (1952).

(10) N. H. Horowitz, M. Ikawa and M. Fling, *Arch. Biochem.*, **25**, 226 (1950).

(11) J. Immers and E. Vasseur, *Acta Chem. Scand.*, **6**, 363 (1952).

(12) D. Rogers, T. E. King and V. Cheldelin, *Proc. Soc. Exptl. Biol. Med.*, **82**, 140 (1953).

(13) W. Stein and S. Moore, *Cold Spring Harbor Symposia Quant. Biol.*, **14**, 179 (1949).

(14) A. Abrams and H. Borsook, *J. Biol. Chem.*, **198**, 205 (1952).

(15) H. Borsook, C. L. Deasy, A. J. Haagen-Smit, G. Keighley and P. Lowy, *ibid.*, **186**, 309 (1950).

(16) H. A. Krebs and K. Henseleit, *Z. physiol. Chem.*, **310**, 33 (1932).

(1) L. C. Maillard, *Compt. rend.*, **154**, 66 (1912).

(2) E. R. Stadtman, *Advances in Food Research*, **1**, 325 (1948).

(3) J. P. Danehy and W. W. Pigman, *ibid.*, **3**, 241 (1951).

(4) A. Gottschalk and S. J. Partidge, *Nature*, **165**, 684 (1950).

(5) C. O. Chichester, F. H. Stadtman and G. Mackinney, *This Journal*, **74**, 3418 (1952).

(6) K. Täufel and H. Iwainsky, *Biochem. Z.*, **323**, 299 (1952).

(7) G. Agren, *C. R. Lab. Carlsberg Ser. chim.*, **28**, 173 (1939).

(8) G. Agren, *Acta Physiol. Scand.*, **1**, 105 (1940).