N,N-Dimethylaniline[23]: $k = 0.014$ min.$^{-1}$; $t_{1/2} = 50$ min.

N-Methylaniline: Very slow; kinetics complicated by appearance of N,N-dimethylaniline, reaching 10% by weight of total amine fraction at end of 1 hr. This means that rate of alkylation of N-methylaniline is faster than its rate of dealkylation, the latter being extremely slow. To demonstrate this, methyl chloride was passed through molten N-methylaniline hydrochloride at 195° and at a flow rate af 154 ml./min. After 3 hr., an aliquot contained 20% tertiary amine. This experiment demonstrates that the reverse reaction, alkylation, is slow under the conditions of dealkylation. Besides being slow it does not become important until the concentration of secondary amine is high.

The Isolation of the Alkyl Bromide from Dealkylation of N,N-Di-*n*-propylaniline.—The effluent hydrogen bromide containing alkyl bromide was passed through an efficient trap cooled with ice–water–salt mixture. The condensate was washed with cold water, separated, and dried. Analysis by gas chromatography (oven temperature, 93°; 10% SE-30 stationary phase, 32 ml./min. He flow rate, retention time for *n*-propyl bromide = 154 sec., retention time for isopropyl bromide = 126 sec.) showed 96% *n*-propyl bromide, 4% isopropyl bromide, and no propylene bromide. Pure *n*-propyl bromide did not isomerize when subjected to conditions identical with isolation procedure.

Demethylation of N-Methyltetrahydroquinoline (Kairoline) to Tetrahydroquinoline.—To show that methyl groups are removed preferentially, kairoline (0.2 mole) was treated with hydrogen chloride at 195° for 13 hr. Recovery of the basic product gave tetrahydroquinoline (0.19 mole, free from tertiary amine as denoted by g.l.c., benzenesulfonamide m.p. 65.6–66.5°, lit. m.p. 67°).

Attempts to Dealkylate Aliphatic Amines.—Regardless of changes in conditions and irrespective of the addition of catalysts or trapping agents such as 4,7-dichloroquinoline or 2,4-dinitrochlorobenzene, the dealkylation of nicotine and of N-methylpiperidine led only to black, polymeric tars. The attempted dealkylation of tri-*n*-butylamine at 195° for 6 hr. gave approximately 1% *n*-butyl bromide.

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[23] One notes that the rate of dealkylation at 195° is about the same as the rate at 177°. Part of this similarity is caused by different flow rates. But, another factor is that hydrogen chloride is not as soluble at higher temperatures in the melt. Thus, an increase in temperature does not necessarily increase the rate appreciably. An experiment to determine the amount of hydrogen chloride dissolved showed that 1 equivalent of hydrogen chloride dissolved per 1 equivalent of amine.

The Swamping Catalyst Effect. V. The Halogenation of Aromatic Acid Derivatives[1]

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A study of the halogenation of the aluminum chloride complexes of acid derivatives using excess aluminum chloride was undertaken. All the following acid derivatives were halogenated as aluminum chloride complexes. Methyl benzoate gave 86% methyl 3-bromobenzoate on monobromination and 89% methyl 2,5-dibromobenzoate on dibromination. *p*-Toluyl chloride gave 85% methyl 3,5-dibromo-4-toluate on dibromination. Methyl *p*-toluate gave 71% 3-chloro-4-toluic acid on chlorination and 65% methyl 3-iodo-4-toluate on iodination. Coumarin gave 74% 6-bromocoumarin. Benzonitrile gave 64% 3-bromobenzonitrile on monobromination and 79% 2,5-dibromobenzonitrile on dibromination. N-Methyl- and N,N-dimethylbenzamides gave poor yields in bromination. Methyl *o*-toluate gave a mixture of halogenated products which could not be separated easily. The preceding procedure is probably the best method of direct introduction of chlorine or bromine into aromatic acid derivatives.

One may ask the question: how is *m*-bromobenzoic acid obtained? The immediate answer would seem to be direct bromination of benzoic acid. This pathway is fraught with obstacles. The halogenation is very slow and incomplete, and the temperature of halogenation is high enough to bring about sublimation of unreacted benzoic acid.[4] To quote one source,[5] "direct halogenation is seldom successful and scarcely ever used" with aromatic acids.

We have now found that direct halogenation of the aromatic acid esters or chlorides can be carried out with eminent success using the swamping catalyst effect as shown.

$$C_6H_5COOCH_3 + 2AlCl_3 + Br_2 \xrightarrow{65°} m\text{-}BrC_6H_4COOCH_3(86\%) + HBr$$

The swamping catalyst effect entails halogenation of the aluminum chloride complex with a highly reactive halogenation species, either X^+ itself, or the ion pair, $X^+\overset{-}{Al}Cl_3X$. The halogenating species cannot be obtained unless more than one equivalent, and preferably two equivalents, of aluminum chloride are used.[6] No solvent is employed.

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[1] Part IV: B. R. Suthers, P. H. Riggins, and D. E. Pearson, *J. Org. Chem.*, **27**, 447 (1962).

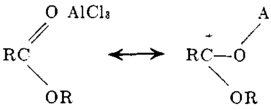
[2] Abstracted mainly from the Ph.D. thesis of W. E. S., 1962.

[3] Abstracted in part from the Ph.D. thesis of B. R. S., 1961.

[4] H. Hubner and G. Weiss, *Ber.*, **6**, 175 (1873): P. S. Varma and P. B. Panicker, *J. Indian Chem. Soc.*, **7**, 503 (1930).

[5] G. M. Dyson, "Manual of Organic Chemistry," Vol. I, Longmans, Green and Co., New York, N. Y., 1950, p. 590.

[6] In an earlier paper,[7] we stated that a unique part of the swamping catalyst effect with ketones was the formation of an eight-membered ring between two moles of acetophenone and two moles of aluminum chloride. From further study of the literature on complexes,[8] we believe that these structures are somewhat variable[9] and it is best to consider the complex simply as a Lewis salt: $R_2C{=}O\ AlCl_3 \longleftrightarrow R_2\overset{+}{C}{-}O\overset{-}{Al}Cl_3$ or



$$RC(=O\,AlCl_3)OR \longleftrightarrow R\overset{+}{C}(OR){-}O{-}\overset{-}{Al}Cl_3$$

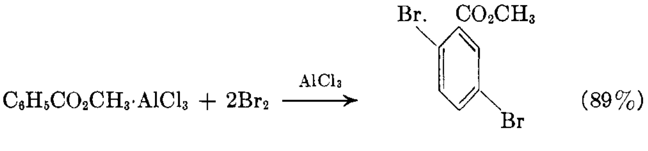
, which may associate to give complexes of higher molecular weight or even dissociate.

[7] D. E. Pearson, H. W. Pope, W. W. Hargrove, and W. E. Stamper, *J. Org. Chem.*, **23**, 1412 (1958).

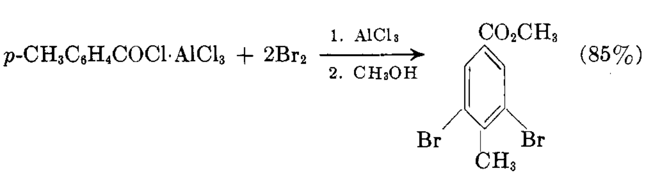
[8] Ester–aluminum chloride complexes: M. F. Lappert, *J. Chem. Soc.* 817 (1961); 542 (1962); J. Vanderhoek, *Baskerville Chem. J. City Coll. N. Y.*, **10**, No. 1, 13 (1960). Acid chloride–aluminum halide complexes: B. N. Menshutkin, *J. Russ. Phys. Chem. Soc.*, **42**, 1310 (1911); E. P. Kohler, *Am. Chem. J.*, **24**, 385 (1900); J. Boeseken, *Rec. trav. chim.*, **19**, 19 (1900); N. N. Lebedev, *Zh. Obshch. Khim.*, **21**, 1788 (1951); *Chem. Abstr.*, **46**, 6586 (1952); W. Nespital, *Z. physik. Chem.* (Leipzig), **16B**, 153 (1932); B. P. Susz and J. J. Whurmann, *Helv. Chim. Acta*, **40**, 971 (1957), and earlier papers. Nitrile–aluminum halide complexes: I. Kablukov and A. S. A. Khanov, *J. Russ. Phys. Chem. Soc.*, **41**, 1755 (1910); *Chem. Abstr.*, **5**, 1419 (1911); R. Müller and G. Wersitsch, *Z. anorg. allgem. Chem.*, **208**, 304 (1932); R. E. Van Dyke and T. S. Harrison, *J. Am. Chem. Soc.*, **73**, 402 (1951).

[9] S. C. J. Olivier, *Rec. trav. chim.*, **37**, 205 (1918); H. Ulich, *Z. physik. Chem.*, Bodenstein-Festband, 423 (1931).

As noted in halogenation of the ketone–aluminum chloride complexes,[7] we found that the acid derivative–aluminum chloride complexes were deactivated toward substitution, gave *meta* oriented products, but had very poor control of the orientation. They behaved as though the directive influence of the complexed group was purely inductive in nature. Any other group attached to the aromatic nucleus seemed to control the orientation. Thus, in the dibromination of methyl benzoate, the reaction was as follows.



The first bromine substitution which is in the *meta* position controls the orientation of the second bromine substitution. But with *p*-toluyl chloride (and very likely with the ester), the reaction was as follows.



The inductive effect of the methyl group, perhaps combined with the small steric effect of the complexed ester grouping, predominates over the orientation influence of the first bromine atom introduced. Chlorination also can be carried out as demonstrated by the preparation of 3-chloro-4-toluic acid in 71% yield. Iodination using iodine monochloride gave methyl 3-iodo-4-toluate in 65% yield. Coumarin, if brominated without complexing with aluminum chloride, yields 3,4-dibromocoumarin which can be dehydrobrominated to 3-bromocoumarin.[10a] The coumarin–aluminum chloride complex, on the other hand, gave 6-bromocoumarin in good yield.[11]

The second question one may ask is whether other methods of directly halogenating aromatic acids are available. The Derbyshire–Waters method[12] is quite comparable in respect to yields and orientation. The only decision to be made is whether one prefers concentrated sulfuric acid and silver sulfate as a medium or anhydrous aluminum chloride.

Considerable literature does exist on the halogenation of acid derivatives using small amounts (or no) catalyst. The chlorination of benzoyl chloride with small amounts of ferric chloride yields a mixture of about 80% *meta*- and 20% *ortho*-chlorobenzoyl chloride.[13] The chlorination of methyl benzoate leads first to benzoyl chloride and then on the addition of ferric chloride to chloro-substituted benzoyl chlorides.[14] Iodination of phthalic anhydride in fuming sulfuric acid of course is a well known process leading to tetraiodophthalic anhydride.[15]

With no many processes available for the halogenation of aromatic acids, one must discriminate among them. We suggest that for laboratory preparation of *meta*-chloro- or bromo-substituted acids the swamping catalyst method be used starting with the ester or acid chloride but for the preparation of *meta*-iodo acids the Derbyshire–Waters method be used.

The swamping catalyst method appears to be quite superior to other methods for preparing *m*-halobenzonitriles. For example in this paper, *m*-bromobenzonitrile was prepared in 64% yield on monobromination and 2,5-dibromobenzonitrile in 79% yield on dibromination. Gas phase bromination of benzonitrile leads to a mixture of monobrominated isomers.[16] *p*-Bromobenzonitrile is obtained in small yield using heterogeneous conditions with sulfuric acid.[17] Earlier reports mention poor yields or complex products from the halogenation of benzonitrile in sealed tubes.[18] None of these results appears comparable to those of the swamping catalyst technique.

Among other acid derivatives investigated in halogenation were N-methyl- and N,N-dimethylbenzamide. They were much more difficult to brominate, particularly N-methylbenzamide. Nevertheless, the *meta*-brominated products were obtained in 30 and 50% yields, respectively.

Experimental

General Procedure.—The apparatus and conditions described in *Organic Syntheses* were employed.[19] Unless otherwise stated, 0.3 mole of acid derivative and 0.8 mole of finely divided, anhydrous aluminum chloride were mixed to form the complex and then 0.35 mole (or 0.7 mole for dihalogenation) of halogen was added dropwise or by passing under the surface.

The halogenated acid chloride complexes, in the halogenation of acid chlorides, were decomposed by dropwise addition of methanol to the flask cooled in ice rather than by transfer of the complex to ice and water. Thus, the halogenated acid chloride complexes were isolated as methyl esters.

Methyl 3-Bromobenzoate.—The gray complex from methyl benzoate and aluminum chloride was brominated smoothly at 60° by dropwise addition of bromine over a period of about 1 hr. The 3-bromo ester was obtained in 85% yield, m.p. 30–31°, after fractionation, b.p. 138–140° at 10 mm., and one recrystallization from hexane.

The red complex from benzoyl chloride and aluminum chloride was brominated in the same manner and after decomposition with methanol yielded 86% methyl 3-bromobenzoate, m.p. 30–31°.

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(10) E. H. Rodd, "Chemistry of Carbon Compounds," Elsevier Publishing Co., New York, N. Y., 1959; (a) Vol. IVB, 877; (b) Vol. IVC, 1569.

(11) A report is given in the literature that bromine water yields 6-bromocoumarin: J. Read and W. G. Reid, *J. Chem. Soc.*, 745 (1928).

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(13) E. Hope and G. C. Riley, *J. Chem. Soc.*, **123**, 2470 (1923); *m*-bromobenzoyl chloride using bromine and chlorine: E. C. Britton and R. M. Tree, U. S. Patent 2,607,802, (Aug. 19, 1952); *Chem. Abstr.*, **47**, 5437 (1953); for chlorination of benzoic acid in a sealed tube, see J. T. Bornwater and A. F. Holleman, *Rec. trav. chim.*, **31**, 221 (1912).

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(19) D. E. Pearson, H. W. Pope, and W. W. Hargrove, *Org. Syn.*, **40**, 7 (1960).

Methyl 2,5-Dibromobenzoate.—Two equivalents of bromine were employed. The crude product was fractionated to remove the monobrominated ester, and the dibrominated ester collected at 94–96° at 0.5 mm., m.p. 39–40° after one recrystallization from hexane. From methyl benzoate the yield was 84%, and from benzoyl chloride it was 45%, the difference in the yield being caused by less complete bromination of the benzoyl chloride complex. A portion of the 2,5-dibromo ester was saponified in 89% yield to 2,5-dibromobenzoic acid, m.p. 154–155°, lit.[20] m.p. 153°.

Methyl 3,5-Dibromo-4-toluate.—The crude product (95 g., b.p. 131–151° at 2 mm.) obtained from 0.3 mole of *p*-toluyl chloride, was recrystallized from methanol several times to yield 78 g. (85%) of methyl 3,5-dibromo-4-toluate, m.p. 87.5–88.5°; sapon. equiv., 311; calcd. 308. A portion of the ester yielded 3,5-dibromo-4-toluic acid, m.p. 238–239° after saponification and recrystallization from methanol, lit.[21] m.p. 235–236°, mixture melting point the same with a sample of the acid prepared from 3,5-dibromo-4-methylacetophenone.[7]

3-Chloro-4-toluic acid.—The chlorination was carried out as described previously[7] starting with methyl *p*-toluate. The reaction mixture was quenched with water rather than methanol and yielded 71% 3-chloro-4-toluic acid, m.p. 201–202° after one recrystallization from aqueous ethanol, lit.[22] m.p. 200–202°.

Methyl 3-Iodo-4-toluate.—Because of the tendency of iodine monochloride to dissociate to chlorine and iodine in the presence of aluminum chloride,[7] the reaction conditions were made as mild as possible. To 0.4 mole of anhydrous aluminum chloride was added 0.13 mole of methyl 4-toluate. The complex was heated to 65°, the usual reaction temperature, and then cooled to room temperature. Iodine monochloride (0.14 mole) was added over a period of 8 hr., the mixture stirred an additional 4 hr. and quenched with 165 g. of methanol added dropwise while the flask was cooled. Fractional distillation of the residue from the dry, neutral ether extract gave 7 g. (26%) of methyl 3-chloro-4-toluate, b.p. 85–87° at 2 mm., n^{25}D 1.5253; and 22 g. (65%) of methyl 3-iodo-4-toluate, m.p. 28–29°, lit.[23] m.p. 28°, sapon. equiv., 279, 281; calcd. 277. The acid melted at 210–211°, lit.[22] m.p. 205–206°.

Attempted Preparation of 5-Bromo-2-toluic Acid.—The bromination of methyl *o*-toluate under swamping conditions led to a mixture of methyl bromo-*o*-toluate esters which could not be separated by fractionation in a Helipak filled column. Both 3-bromo- and 5-bromo-2-toluic acids were isolated in poor yield from the saponified mixture. Chlorination of methyl *o*-toluate also gave an inseparable mixture.

6-Bromocoumarin.—The crude product was collected at 144–155° (1 mm.). It was recrystallized from ethanol to obtain 74% of colorless, fine needles, m.p. 165–166°, lit.[24] m.p. 164°. The mixture melting point with a sample made from the Perkin condensation of 5-bromosalicylaldehyde and acetic anhydride was also the same. 3,4,6-Tribromocoumarin, m.p. 318–319°, was made from 6-bromocoumarin and bromine in carbon bisulfide, lit.[24] m.p. 316°.

3-Bromobenzonitrile.—The yellow complex between benzonitrile (0.43 mole) and aluminum chloride (0.85 mole) was brominated at 60° using 0.43 mole of bromine. The addition took 30 min. and was followed by a heating period of 11 hr. (probably an excessive heating time). Benzonitrile (8 g., 19%) was removed at 46–50° (2 mm.) and the residue dissolved in hexane, decolorized with Norit, and chilled. After filtration and air-drying 3-bromobenzonitrile (50 g., 64%) was obtained, m.p. 37–38°, lit.[25] m.p. 38°. The benzamide, prepared from the nitrile, melted at 156–156.5°, lit.[22] m.p. 155°. When the bromination was run with iron as a catalyst, in place of aluminum chloride, only benzonitrile and *sym*-triphenyltriazine (27%, m.p. 231–232°, lit.[10b] m.p. the same) were obtained.

2,5-Dibromobenzonitrile.—The ratios of reagents were aluminum chloride 3.5 moles, benzonitrile 1.1 moles and bromine 3.1 moles. The bromine addition was carried out at 60° for 3 hr. followed by another 3-hr. heating period. The product was distilled up to 120° (2 mm.). The distillate was fractionally crystallized from benzene to yield 235 g. (79%) of 2,5-dibromobenzonitrile, m.p. 144–145°, lit.[26] m.p. 132°.

Anal. Calcd. for $C_7H_3Br_2N$: Br, 61.2. Found: Br, 61.2.

2,5-Dibromobenzoic acid, m.p. 156–157°, lit.[20] m.p. 153°, was obtained by hydrolysis of the nitrile. 2,5-Dibromoacetophenone, m.p. 40–41°, lit.[20] m.p. the same, was prepared from the nitrile by addition of methylmagnesium iodide. The oxime, m.p. 139–140°, was rearranged to 2,5-dibromoacetanilide, m.p. 171–172°, lit.[28] m.p. the same. The infrared spectrum of 2,5-dibromobenzonitrile showed a peak at 820 cm.$^{-1}$ and none at 780 cm.$^{-1}$, which is to be expected of two adjacent aromatic hydrogens.

Competitive Bromination of Acetophenone with Methyl Benzoate and with Benzoyl Chloride under Swamping Conditions.—A mixture of acetophenone (0.05 mole) and methyl benzoate (0.05 mole) was added dropwise to aluminum chloride (0.2 mole). While the fluid complex was maintained at 65°, bromine (0.05 mole) was added dropwise in 95 min. Gas chromatography of the four components,[29] the two starting materials, *m*-bromoacetophenone, and methyl *m*-bromobenzoate indicated that methyl benzoate was brominated at least twice as readily as acetophenone. Similarly, it was shown that acetophenone was brominated at least twice as rapidly as benzoyl chloride.

3-Bromo-N-methylbenzamide.—The green complex of N-methylbenzamide and aluminum chloride did not brominate at temperatures lower than 120°. With the higher temperature of reaction more tar was obtained. However, 3-bromo-N-methylbenzamide was isolated in 30% yield, m.p. 96–97° from aqueous methanol, mixture melting point with a sample prepared from *m*-bromobenzoyl chloride and methylamine the same.

3-Bromo-N,N-dimethylbenzamide.—The brown complex between aluminum chloride and N,N-dimethylbenzamide was brominated at 75°. The titled compound was obtained in 50% yield m.p. 52–53°, mixture melting point with an authentic sample from *meta*-bromobenzoyl chloride and dimethylamine the same.

Anal. Calcd. for $C_9H_{10}BrNO$: Br, 35.1. Found: Br, 35.7.

3-Bromo-4-ethylacetophenone.—By the regular procedure[19] this compound was obtained in 59% yield, b.p. 106–107° at 1.7 mm., n^{25}D 1.5669.

Anal. Calcd. for $C_{10}H_{11}BrO$: Br, 35.2. Found: Br, 35.2.

The oxime from hexane melted at 70–70.5° and the 2,4-dinitrophenylhydrazone at 194–194.5°.

Acknowledgment.—We are indebted to the National Science Foundation for a grant in support of this work.

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