LXI.—*The Laws of Aromatic Substitution. Part VI. A Quantitative Method for the Rapid Determination of Isomeric Nitro-derivatives of Laterally Substituted Toluenes.*

By BERNHARD FLÜRSCHEIM and ERIC LEIGHTON HOLMES.

INVESTIGATIONS on the influence of substituted methyl groups on the positions taken by nitro-groups entering the nucleus are generally faced with two problems : uniform oxidation of all the isomerides to the corresponding acids, and accurate determination of the relative proportion of *o*- and *p*-nitrobenzoic acids on the one hand and *m*-nitrobenzoic acid on the other.

I. *Oxidation.*—(A) *Permanganate.* As long ago as 1877, Michael and Norton (*Ber.*, **10**, 580) stated that *p*-nitrotoluene gives a good yield of *p*-nitrobenzoic acid when boiled with a solution of 1 part of permanganate in 40 parts of water. Actual figures, or the comparative yields obtained on oxidation of isomeric nitrotoluenes, were, however, not given. In Part V of this series (J., 1926, 1562) we showed that, when an even weaker solution (for instance 1 : 60) was employed, the acids were obtained in yields of about 80% of the theoretical and, what is more important, that the percentages were practically identical for all three nitro-isomerides. These results have since been utilised by Ingold and his co-workers.

We have applied the method to a large number of compounds (see chiefly Parts VIII, IX, and X of this series) without a single failure. In two cases (phenylnitromethane and ethyl phenylbromomalonate), the dilution being 1 : 60, *gradual* addition of the permanganate produced a less pure, yellow acid mixture, whereas the usual colourless product was obtained when the permanganate had been added all at once. In some experiments involving specially mobile substituents, certain modifications were introduced (see following paper). The method is simplified by destroying the residual permanganate with sulphur dioxide, which simultaneously dissolves the manganese dioxide, filtration being thus obviated.

(B) *Dilute nitric acid.* Nitric acid (*d* 1·10—1·15) was employed by Baker and Ingold (J., 1926, 2468) for the oxidation of nitration products. This agent is not of such general applicability as permanganate (see following paper), but where it can be used our tests prove it to be equally satisfactory. The resistance to destructive oxidation is again almost identical for the isomeric acids, and is much the same as with permanganate (see experimental part). Baker and Ingold's statement that benzoic acid is not nitrated under these conditions is essentially correct; our more delicate method, however, has enabled us to show that nitration under Baker and Ingold's average conditions takes place to the extent of about 1%.

II. *Determination of the Proportion of the Isomerides.*—Francis and Hill (*J. Amer. Chem. Soc.*, 1924, **46**, 2498) devised a method for estimating the percentages of *o*- + *p*- and of *m*-nitrobenzoic acids based on the consumption of two atoms of bromine by the former acids and of three atoms of bromine by the latter acid after reduction to amino-acids. These authors also directed attention to a source of error, due to partial replacement of carboxyl by bromine, resulting in an increased consumption of bromine. The method, therefore, could give trustworthy results only if the degree of such replacement were always the same for a given mode of operating. But since the three amino-acids and their partly brominated derivatives cannot all be assumed to take up bromine at the same rate, it seems clear that the extent to which carboxyl is eliminated from the *o*- and *p*-acids must vary, even under otherwise similar conditions, with the initial composition of the mixture—and, whenever an intermediate solid phase is formed, also with unavoidable physical differences. It is not surprising, therefore, that Ingold and his co-workers appear to have abandoned this method in favour of more laborious processes, including the removal of benzoic acid by sublimation and the old method of barium-salt precipitation and fractional recrystallisation, which we ourselves had utilised in Part V of this series. These tedious separations, however (and this applies to the solubility method also), do not give even approximately accurate results when certain substances—such as the bromo- and nitrobromo-acids encountered in Part VII—are present, and therefore the discovery of a better method became imperative. A suggestion made by Mr. W. B. Saville, that *m*-bromobenzoic and benzoic acids might be separated from nitro-acids after reduction of the latter with titanous chloride (which would render them soluble in dilute acid), led us to consider the feasibility of separating the amino-acids from one another by introducing a difference in their behaviour towards acids or alkalis. No difficulty was experienced in converting *o*- and *p*-aminobenzoic acids at room temperature * *quantitatively* into tribromoaniline by prolonged exposure to bromine in dilute hydrochloric acid, and separation from the tribromo-*m*-aminobenzoic acid simultaneously formed from *m*-aminobenzoic acid was then easily effected by alkaline reagents. *Whereas, therefore, by Francis and Hill's method* three *bromine atoms are introduced into one of the aminobenzoic acids, and* two *(plus an indeterminate fraction) into the other two, and the bromine consumption constitutes the measure, by our method all three acids take up* exactly three *atoms of bromine, and the actual weights of the two compounds, formed with a high degree of purity, are the measure.*

EXPERIMENTAL.

I. *Oxidation.*—(A) *Resistance of acids to permanganate.* (a) 0·50 G. of benzoic acid was boiled for 3 hours with 1 g. of potassium per-

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* Francis and Hill (*loc. cit.*, p. 2500) observed quantitative conversion of *o*- and *p*-aminobenzoic acids into tribromoaniline only at temperatures above 40°, and at the ordinary temperature only in the presence of sufficient alcohol to prevent precipitation of intermediate compounds. A *gravimetric* method was suggested by these authors only for hydroxybenzoic and aminosulphonic acids. It differs in principle from our method and, moreover, could not be applied to our problems, since it depends, not on selective salt formation as in our case, but on the—comparatively rare—occurrence of complete selective solubility in the absence of salt formation.

manganate in 60 c.c. of water and 2·5 c.c. of 10% aqueous potassium hydroxide. 0·447 G. (89·4%) of benzoic acid was recovered.

(b) 0·50 G. of *m*-bromobenzoic acid was treated as described above, but with only 1·6 c.c. of potash solution. Recovery = 0·452 g. = 90·4%.

(c) 0·25 G. of each of the three nitrobenzoic acids were mixed and boiled for 3 hours with 1·5 g. of permanganate in 90 c.c. of water and 2·5 c.c. of 10% aqueous potassium hydroxide. Recovery = 0·602 g. = 80·3%.

The yield of nitrobenzoic acids obtained on oxidation of a mixture of laterally substituted nitrotoluenes is, as a rule, higher than the recoveries recorded above, because the permanganate solution becomes more and more exhausted as the concentration of the acids formed increases.

(B) *Resistance of acids to nitric acid* (*d* 1·1244—1·1253). (a) 1 G. of benzoic acid was boiled for 6 hours with 50 c.c. of nitric acid (*d* 1·1244). The recovered acids, on reduction and bromination as described under II, gave 0·904 g. of benzoic acid, 0·003 g. of tribromoaniline, and 0·031 g. of tribromo-*m*-aminobenzoic acid (= 0·014 g. of *m*-nitrobenzoic acid).

(b) 0·25 G. of each of the three nitrobenzoic acids and 0·25 g. of benzoic acid were boiled together for 6 hours with 50 c.c. of nitric acid (*d* 1·1253). The recovered acids yielded 0·237 g. of benzoic acid (94·8% recovery), 0·814 g. of tribromoaniline (= 0·412 g. of *o*- + *p*-nitro-acids : 82·4% recovery), and 0·462 g. of tribromo-*m*-aminobenzoic acid (= 0·206 g. of *m*-nitro-acid : 82·4% recovery). Baker and Ingold (*loc. cit.*) employed acid of *d* 1·10—1·15 and boiled the solutions for 2—10 hours.

II. *Determination of the Proportion of the Isomerides.*—The acids are boiled with sufficient 10% hydrochloric acid to dissolve them, and aqueous titanous chloride (Knecht and Hibbert's method; also used by Francis and Hill) is then added until, after 10 minutes' boiling, the solution is still coloured. After cooling to room temperature, any non-amino-acids present (benzoic, bromobenzoic, etc.) are removed by ether. (Ether is the most suitable solvent for benzoic acid, because loss by volatility is minimised; for other mixtures other solvents, such as chloroform, may be found preferable.) After air has been bubbled through the aqueous liquid to remove all the ether, bromine water is added in not too large excess, and the mixture is left for 24 hours at room temperature, initially with occasional shaking. Any solid is then filtered off, washed with water, then several times with potassium bicarbonate solution and again with water, and dried to constant weight at 80° (at 100° it slowly sublimes). This is 2 : 4 : 6-tribromoaniline. The acid mother-liquor of this precipitate is freed from bromine by a current of air and twice extracted with ether, and the extracts are shaken with an excess of bicarbonate solution, dried, and evaporated, yielding a further quantity of tribromoaniline. The several bicarbonate extracts are united and acidified, and 2 : 4 : 6-tribromo-3-aminobenzoic acid is then obtained, partly as a precipitate and partly by extraction of the filtrate therefrom with ether.

A special test showed that no appreciable portion of the aminobenzoic acids is withdrawn from the acid solution by the ether : 1 g. of a mixture of equal parts of the three nitrobenzoic acids was reduced and then twice extracted with ether as usual; the extracts left only 0·004 g. (oil) on evaporation.

When, in addition to aminobenzoic and non-aminobenzoic acids, a "negatively" substituted aminobenzoic acid, the salt of which with an inorganic acid would be largely dissociated in dilute solution, is present, its amount can be determined by a slight variation of the above procedure. If, for instance, bromoamino-acids (compare Part VII) are present, the solution of the initial mixture of reduced acids is repeatedly shaken with ether, until not more than 0·001 g. per g. of the original mixture of unreduced acids is extracted (in Part VII, 4 extractions were necessary in the case of 24-hour nitrations, and 8 for 10-day nitrations). The united ethereal extracts are washed with 15—20 c.c. of 10% hydrochloric acid, and this acid extract is shaken once with ether and then added to the main aqueous portion before bromination. The combined ethereal extracts are dried and, after addition of 10 c.c. of glacial acetic acid, distilled until no ether is left; the residual solution, after addition of 2 c.c. of bromine per g. of the original mixture, is kept for 24 hours, then diluted with water, and freed from bromine by a current of air. Any precipitate produced by the dilution is filtered off, before the bromine is removed, and is washed with bicarbonate solution; this leaves undissolved a portion of the tribromoaniline produced from the bromonitro-acid. The remainder of such tribromoaniline is obtained by adding an excess of bicarbonate to the filtrate from the above precipitate, shaking the solution with ether, and drying and evaporating the ethereal extract. All the alkaline liquors are now united, acidified, and shaken with ether, whereby the non-amino-acids (*e.g.*, benzoic and bromobenzoic acids) are obtained.

III. *Results with Synthetic Mixtures.*—

	I.			II.			III.		
Acids.	% Taken.		% Found.	% Taken.		% Found.	% Taken.		% Found.
m-Bromobenzoic	10·02	50·12	49·65	0		0	0		0
Benzoic	40·10			34·30		34·62	31·26		32·01
o-Nitrobenzoic ...	0	40·15	40·75	19·19	40·05	40·28	15·18	34·48	34·51
p-Nitrobenzoic ...	40·15			20·86			19·30		
m-Nitrobenzoic ...	9·73		9·60	25·65		25·10	34·26		33·48
	100·00		100·00	100·00		100·00	100·00		100·00

The figures under "% Found" are percentages of the total yield.

In II and III, the results were obtained without prior disclosure of the compositions of the mixtures.

A sample of purchased " pure " *m*-nitrobenzoic acid (m. p. 138—139°, instead of 141°) gave, when ground and heated for 4½ hours at 100° before weighing, reduction, and bromination, 2·227 g. of tribromoaminobenzoic acid and 0·009 g. of tribromoaniline per g. of material, equivalent to 99·44% of *m*-nitrobenzoic and 0·45% of *o*- and *p*-nitrobenzoic acids.

IV. *Calculation of Molecular Percentages.*—In the above tests, special care was taken to avoid volatilisation of benzoic acid. But quicker working is possible if, in the absence of other volatile materials, the weight of benzoic acid is calculated by difference. In Part VII, for instance, from the weights of the tribromoaniline produced from nitrobenzoic acids, of the tribromoaniline from bromonitro-acids, and of the tribromoaminobenzoic acid, the weights of *p*-(*o*-)nitrobenzoic, bromonitrobenzoic and *m*-nitrobenzoic acids, respectively, in the original mixture were calculated. From a bromine analysis of the original mixture the corresponding weight of bromobenzoic acid was calculated, from which, by subtraction of the bromonitrobenzoic acid—also calculated as bromobenzoic acid—the weight of un-nitrated bromo-acid was obtained. The difference between the weight of the original acid mixture and the sum of the calculated weights of all these fractions gave the weight of benzoic acid. From these figures the molecular percentages were calculated in the usual way.

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