LETTERS TO THE EDITORS

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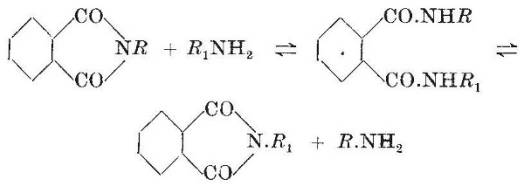
Composition of the Antimalarial Drug *R*.63 and the Ing and Manske Hydrazine Hydrolysis of N-Substituted Phthalimides

DURING 1944, we investigated, as part of our antimalarial research programme, the structure of the potent antimalarial drug *R*.63[1]. The recent publication by Mosher[2] of a further contribution to this subject makes it desirable to report briefly our own results. Some of this work forms the subject-matter of a British Patent Application (17071/44, of September 6, 1944) which was placed on the secret list, thus delaying publication. It is clear that Mosher has independently reached the same conclusion as our own, namely, that *R*.63 contains a substantial proportion of *R*.36 (8-γ-aminopropylamino-6-methoxyquinoline dihydrochloride).

Our preliminary experiments soon indicated that *R*.63 was a complex mixture, and we therefore approached the problem mainly by a study of the reactions involved in its preparation, in preference to attempting a complete analysis of *R*.63 with few clues to the nature of the probable constituents. In our preparations of *R*.36 by the hydrolysis of 8-γ-phthalimidopropylamino-6-methoxyquinoline with alcoholic hydrazine hydrate[3], we have found that a secondary product, *bis*-[γ-(6-methoxy-8-quinolylamino)propyl]-phthalamide, is formed in amounts depending on the proportion of hydrazine hydrate used (30 per cent theoretical quantity with 0·8 molecular proportion of hydrazine hydrate). The discovery of this by-product led eventually to the following scheme of reactions between N-substituted phthalimides and amines being established.

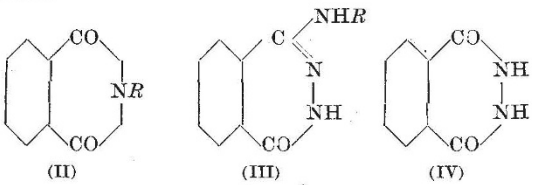


The main factors which determine the end products are the electronic characteristics of R and R_1 and such relevant properties as solubility of their derivatives in the reagents used, or volatility at the reaction temperature.

When the penultimate stage of the preparation of *R*.63 (the fusion of 8-γ-aminopropylamino-6-methoxyquinoline and γ-bromopropyl phthalimide) was considered in the light of the above scheme, it was possible to explain such unexpected results as the isolation from the reaction product of some 8-γ-phthalimidopropylamino-6-methoxy quinoline (I)—a result confirmed but not explained by Mosher. The isolation of (I) implied the simultaneous formation of the highly reactive bifunctional compound, γ-bromopropylamine, which would immediately undergo self-condensation or react with other components of the reaction mixture. Evidence for this view was found in a model experiment in which *n*-propylamine was in fact liberated from *n*-propylphthalimide. Furthermore, unchanged starting materials and some of the required product, 8-γ'-phthalimidopropyl-γ-aminopropylamino-6-methoxyquinoline, were found in the fusion melt. At this point, it was clear that the final stage in the *R*.63 preparation (treatment of the crude fusion melt with alcoholic hydrazine hydrate followed by warm dilute hydrochloric acid) could lead to an even more complex mixture of products. We therefore turned our attention to the synthesis for antimalarial test of those impurities likely to be present in *R*.63 as the result of the side reactions brought to light in our work.

The possibility of radical exchange during phthalimidoalkylation reactions used to build up side chains for antimalarial compounds is a factor to be assessed before structure can be assigned with certainty to the products obtained.

A further interesting feature which also emerged was the nature of the intermediate formed in the hydrazine hydrolysis of *N*-substituted phthalimides (II). Ing and Manske[4] tentatively assigned the structure (III) to the product, but did not isolate and characterize it in any one case.



(II) (III) (IV)

We have found that the product is in fact the *salt* of the base, $R.NH_2$, with phthalyl hydrazide (IV), which is a moderately strong acid. The recognition of the nature of this intermediate (foreshadowed by Mosher, *loc. cit.*) shows at once that the subsequent acid hydrolysis is an irrelevant step, and improvements in the method which may widen its application are apparent. Thus, the required base can be obtained by thermal dissociation, by solvent extraction or by basification of the intermediate salt. An interesting new application of phthalyl hydrazide is the preparation of anhydrous hydrazine by thermal dissociation of the readily accessible hydrazine salt of phthalyl hydrazide[5]. Other volatile bases may be treated similarly.

A fuller account of this work will appear elsewhere in due course.

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[1] Robinson and Tomlinson, *J. Chem. Soc.*, 1524 (1934). Robinson *et al.*, *J. Chem. Soc.*, 555 *et seq.* (1943).
[2] Mosher, *J. Amer. Chem. Soc.*, 1565 (1946).
[3] Baldwin, *J. Chem. Soc.*, 2962 (1929). Magidson and Bobishev, *J. Gen. Chem., U.S.S.R.*, **8**, 912 (1938). Beer, *J. Gen. Chem., U.S.S.R.*, **9**, 2158 (1939). Robinson *et al.*, see ref. 1. Kissinger, Von, and Carmack, *J. Amer. Chem. Soc.*, 1563 (1946). Mosher, see ref. 2.
[4] Ing and Manske, *J. Chem. Soc.*, 2349 (1926).
[5] Brit. Pat. Applic., 27900/46.

Kinetics of Aromatic Nitration: the Nitracidium Ion

THE kinetic studies described in the first of these communications* lead to the conclusion that the nitracidium and nitronium ions, $H_2NO_3^+$ and NO_2^+, are successively formed during nitration by nitric acid, but that only the nitronium ion, NO_2^+, is effective for nitration in anhydrous or nearly anhydrous acid. This note offers evidence for the effectiveness, under other conditions, of the nitracidium ion, $H_2NO_3^+$, as a nitrating agent.

We should expect to be able to provide such evidence, if at all, only by operating in aqueous media. For it has been shown that in anhydrous nitric acid, as well as in other anhydrous strong acids, any $H_2NO_3^+$ formed is largely or completely dehydrated to NO_2^+; and we can be certain that, whenever any appreciable quantity of NO_2^+ is present, it, rather than $H_2NO_3^+$, will be the effective agent for nitration.

We have accordingly pursued the study of nitration kinetics into the range of media in which the main constituent is water, though the concentration of nitric acid has to be such that this substance is largely present as molecules, and not almost wholly as nitrate ions. Under these conditions nitration is invariably (within our experience) a reaction of the first order with respect to the aromatic compound: comment on this is made below. Further, the reaction is accelerated by added strong acids, such as perchloric or sulphuric acid: this shows that the nitric acid molecule itself is not the nitrating agent, and that a proton uptake must in some way be involved. Finally, nitration is retarded by added nitrate ions, and this is not a primary salt effect. All these results point to the formation of the nitracidium ion in pre-equilibrium,

$$2HNO_3 \rightleftharpoons H_2NO_3^+ + NO_3^-,$$

and they are consistent with the hypothesis that this ion is the nitrating agent.

The kinetic results do not rigorously exclude the possibility that the nitracidium ion is further converted into the nitronium ion, and that the latter is the nitrating agent. There are, however, two arguments against this interpretation. One is that our knowledge of the properties of the NO_2^+ ion make it very difficult to believe that any trace of it could exist in a medium containing 70 mol. per cent of water. The other is that, if the NO_2^+ ion were an intermediary, we might have hoped to observe a zeroth-order reaction, for which, actually, we have made a prolonged but unavailing search. We have evidence that the nitracidium ion may also become the effective agent for the *N*-nitration of amines[1].

The main series of experiments have been carried out with sodium toluene-ω-sulphonate. Because of the small nitrating power of solutions such as those here used, it is necessary to employ reactive aromatic compounds, which must, moreover, be soluble in water. Phenol and aniline derivatives had to be avoided, because special complications are liable to arise in these cases.

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* *Nature*, **158**, 448 (1946).
[1] Unpublished investigations with J. Glazer.

Nitration of Phenol and Aniline Derivatives: Role of Nitrous Acid

WHILE nitrous acid (we include in this term all material that with water gives nitrous acid) is a negative catalyst in aromatic nitration generally, it has often been found to be a positive catalyst in the nuclear nitration of phenol and aniline derivatives. New experiments, mainly with phenol derivatives, have lessened the contrast by showing that, in the nitration of these substances, both positive and negative catalysis may be encountered in different ranges of nitric acid concentration, and that the negative catalysis is quite similar to that appearing in the nitration of aromatic compounds of other types. Nevertheless it is clear that certain special mechanisms, dependent on nitrous acid, intervene in the nitration of phenol and aniline derivatives, and we have been attempting to throw some light on their nature by a study of the kinetics and products of the nitration of these compounds.

The following is a composite kinetic picture based on studies with phenol, *o*- and *p*-nitro- and 2 : 4-dinitro-phenol, anisole, *p*-cresyl methyl ether and diphenyl ether, mainly in acetic acid as solvent. Parts of the pattern become repressed, and other parts accentuated, for aniline derivatives. For fixed concentrations of nitrous acid, an increasing concentration of nitric acid at first retards, then strongly