

**547.** *Aliphatic Hydroxylamines. Part III.\* Reaction with Diazotised Aromatic Amines. A Novel Synthesis of Acylbenzenes from the Corresponding Amine.*

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The behaviour of *NN*-dialkylhydroxylamines on autoxidation leads to the prediction that they would condense with diazotised aromatic amines, but only in strongly alkaline media. In agreement with prediction, the products are found to include dialkylamines and alkyl aryl ketones. In the special case of dimethylhydroxylamine, the products include diaryl ketones in addition to dimethylarylamines and aromatic aldehydes.

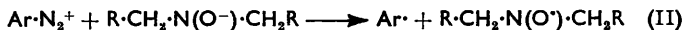
IN Part II,<sup>1</sup> reasons were given for believing that the autoxidation of *NN*-dialkylhydroxylamines proceeds, at least in part, by a one-electron stage, there being formed a radical-ion (III) which had enhanced stability (compared with an alkyl radical) in aqueous solution and in which the free-radical character was spread over the C–N–O system. It was recognised that many oxidations would not stop at the one-electron stage, but would proceed further, and by the removal of a second electron would form the nitron. But, because some organic peroxide was formed in the autoxidation process, it was hoped that some other system could be found which would oxidise (at least in part) by a single-electron process, and so confirm the conclusions reached as a result of the work on autoxidation. It was eventually concluded that the reaction between aromatic diazonium compounds and *NN* dialkylhydroxylamines in aqueous sodium hydroxide should fulfil the conditions and would be diagnostic of the one-electron process. These conditions were : (1) The reaction must be capable of being carried out in aqueous alkali in order to ensure an adequate concentration of the ion  $(R\cdot CH_2)_2NO^-$ . (2) The agent must be only weakly oxidising, or a two-electron transfer would be favoured, with consequent formation of nitron. (3) The oxidising agent must itself be reduced to a radical which must not bear a negative charge

\* Part II, *J.*, 1956, 1093.

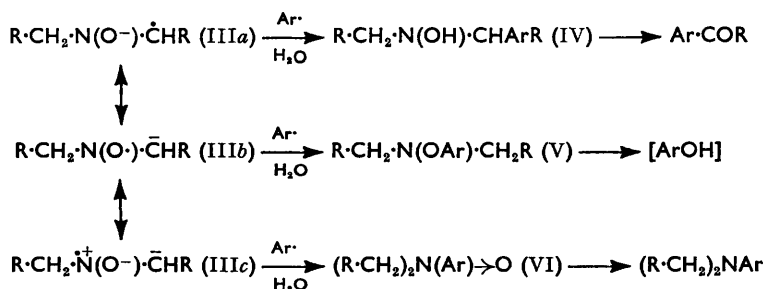
<sup>1</sup> Johnson, Rogers, and Trappe, *J.*, 1956, 1093.

(which would hinder approach to, and combination with, the radical anion) and must have a life in the medium sufficient to find and combine with a hydroxylamine radical-ion. (4) The products of combination of the two radicals in the predicted ways must be capable of recognition and preferably of isolation.

The oxidising properties of aromatic diazonium salts appear to be of the right order.<sup>2</sup> It might be difficult to say with certainty exactly what species was concerned in a reaction of an aromatic diazonium salt under the strongly alkaline conditions required, and indeed substitution in the aromatic ring might alter the nature of the reacting species, because of the known variations in the rate of formation of diazoates; but, if this point is disregarded, the process may be considered analogous to the first step in the uncatalysed replacement of the diazonium radical by iodine,<sup>3</sup>  $\text{ArN}_2\text{Cl} + \text{HI} \longrightarrow \text{Ar}\cdot + \text{N}_2 + \text{I}_2 \longrightarrow \text{ArI}$ , or the reduction of diazonium salts by hypophosphorous acid.<sup>4</sup> Even though the equation probably does not accurately represent the aryl species, the overall reaction predicted is:



The radical (II) is now transformed by an intermolecular process (Part II) into the radical ion (III) which then combines, in one of its three forms (IIIa—c), with  $\text{Ar}\cdot$ :



In practice none of the three possible products (IV)—(VI) has been isolated as such, but obvious derivatives from two of them have been shown to be formed in substantial amounts, alkyl aryl ketones from (IV), and dialkylarylamines from (VI). Phenols would be the predicted derivatives from (IIIb), and in the simplest case phenol has been isolated, but this is of little diagnostic value.

Little earlier work on the reaction of aromatic diazonium compounds with alkylhydroxylamines has been reported. Drum, O'Connor, and Reilly<sup>5</sup> found that mono-*N*-alkylhydroxylamines condensed under alkaline conditions, to give *N*-hydroxydiazoamino-compounds,  $\text{Ar}\cdot\text{N}:\text{N}\cdot\text{NR}\cdot\text{OH}$ , which were exactly analogous to diazoamino-compounds made from simple secondary amines in that they regenerated their components on acidification. Boese, Jones, and Major<sup>6</sup> attempted the condensation of aromatic diazonium salts with dimethylhydroxylamine in aqueous acid solution and got only tar; it is now easy to see why; concentrated alkali is essential for the formation of the radical ion (III), as was deduced from autoxidation experiments (Part II). It has now been found that, when a solution of a diazonium salt is run into aqueous dialkylhydroxylamine in the presence of excess of sodium hydroxide, condensation is almost instantaneous, as shown by the loss of diazo-coupling ability. Later, it was found to be much more convenient to mix the diazonium chloride with an aqueous solution of the hydroxylamine hydrochloride, under which conditions there is no reaction, and to run the mixture into aqueous sodium hydroxide. If the mixture so formed from the condensation of benzenediazonium chloride and diethylhydroxylamine was acidified immediately and distilled in steam, the distillate contained acetophenone, together with a small amount of acetophenone oxime.

<sup>2</sup> Saunders, "The Aromatic Diazo Compounds," Arnold, London, 1949, p. 111.

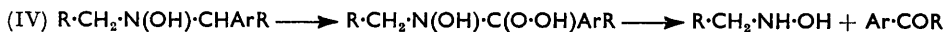
<sup>3</sup> *Idem*, *op. cit.*, p. 113.

<sup>4</sup> Kornblum, Cooper, and Taylor, *J. Amer. Chem. Soc.*, 1950, **72**, 3013.

<sup>5</sup> Drum, O'Connor, and Reilly, *Sci. Proc. Roy. Dublin Soc.*, 1940, **22**, 273; see also Bamberger and Renaud, *Ber.*, 1897, **30**, 2285.

<sup>6</sup> Boese, Jones, and Major, *J. Amer. Chem. Soc.*, 1931, **53**, 3530.

Once the oxime had been established as one of the products of the reaction, formed (as far as could be judged) as an intermediate in the formation of ketone, and not as an artefact from ketone and hydroxylamine (which could conceivably have been formed in some other way), a revision of certain preconceived ideas about the mechanism had to be made. It had seemed probable that the monoarylated hydroxylamine (IV) would undergo any further oxidation at the carbon bearing the aryl group. This oxidation could be an autoxidation:



(cf. Part II) or a further oxidation by diazonium salt. It was found that when air was blown into the mixture for several hours immediately after the condensation was complete and before the acidification the yield of acetophenone was improved. But oxidation on the arylated carbon atom alone could not give oxime, and it has been necessary to conclude that the second oxidation stage takes place, surprisingly, on the unarylated carbon atom:



With this probable mechanism in mind, a reliable method of working up the product has been developed (see p. 2788). Table 1 records the yields obtained in this way from a

TABLE 1. *Reaction between diazotised amine R'·C<sub>6</sub>H<sub>4</sub>·NH<sub>2</sub> and dialkylhydroxylamine R<sub>2</sub>N·OH.*

R'	R	Product	B. p. (°/mm.)	Yield (%)	Derivatives *
H	Et	Ph·COMe	200—204°	38	D, m. p. 228—230°. O, m. p. 58—59°.
<i>o</i> -Cl	Et	<i>o</i> -Cl·C <sub>6</sub> H <sub>4</sub> ·COMe	110—117/20	16	O, m. p. 112—113°
<i>m</i> -Cl	Et	<i>m</i> -Cl·C <sub>6</sub> H <sub>4</sub> ·COMe	110—117/16	29	O, m. p. 88—89°. N, m. p. 176°. S, m. p. 232°
<i>p</i> -Cl	Et	<i>p</i> -Cl·C <sub>6</sub> H <sub>4</sub> ·COMe	136—145/40	31	S, m. p. 200—201°
<i>p</i> -Me	Et	<i>p</i> -Me·C <sub>6</sub> H <sub>4</sub> ·COMe	108—113/20	24	O, m. p. 88°
<i>p</i> -OMe	Et	<i>p</i> -MeO·C <sub>6</sub> H <sub>4</sub> ·COMe	145—150/25	18	O, m. p. 87°
<i>o</i> -NO <sub>2</sub>	Et	<i>o</i> -NO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub> ·COMe	—	4·7 <sup>a</sup>	D, m. p. 224—225° <sup>b</sup>
<i>p</i> -NO <sub>2</sub>	Et	<i>p</i> -NO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub> ·COMe	—	12·5 <sup>c</sup>	
H	Pr <sup>n</sup>	Ph·COEt	90—101/16	39	S, m. p. 176—177°
<i>p</i> -Cl	Pr <sup>n</sup>	<i>p</i> -Cl·C <sub>6</sub> H <sub>4</sub> ·COEt	137—144/31	20 <sup>d</sup>	S, m. p. 173—174°
<i>p</i> -Me	Pr <sup>n</sup>	<i>p</i> -Me·C <sub>6</sub> H <sub>4</sub> ·COEt	117—119/18	35·5	O, m. p. 87—90°
<i>p</i> -NO <sub>2</sub>	Pr <sup>n</sup>	<i>p</i> -NO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub> ·COEt	—	9 <sup>e</sup>	
<i>p</i> -Cl	Bu <sup>n</sup>	<i>p</i> -Cl·C <sub>6</sub> H <sub>4</sub> ·COPr <sup>n</sup>	136—138/22 <sup>f</sup>	26·5	N, m. p. 173°

\* D = 2 : 4-dinitrophenylhydrazone; O = oxime; N = *p*-nitrophenylhydrazone; S = semicarbazone.

<sup>a</sup> Isolated as the derivative. <sup>b</sup> Found : N, 20·0. C<sub>14</sub>H<sub>11</sub>O<sub>6</sub>N<sub>5</sub> requires N, 20·3%. <sup>c</sup> Isolated as solid, m. p. 77—78°. <sup>d</sup> In this early experiment the diazonium salt solution was run into a mixture of the hydroxylamine and aqueous alkali. <sup>e</sup> Isolated as the solid, m. p. 88—89°. <sup>f</sup> M. p. 35—36°.

variety of aromatic diazonium salts condensed with diethyl-, dipropyl-, and dibutylhydroxylamine. The method is inferior to that described by Beech,<sup>7</sup> though it might find application in favourable cases, *e.g.*, for the preparation of aryl ethyl ketones. It is considerably less efficient than Beech's for the preparation of aldehydes for several reasons, one of which throws further light on the mechanism of the reaction.

A postulated intermediate in the formation of alkyl aryl ketone is a monoarylated hydroxylamine. There seems no particular reason why this hydroxylamine should not react a second time, and on the same carbon atom, to give a diarylated hydroxylamine. When diethylhydroxylamine is used, the product would not be oxidised and hydrolysed to aromatic carbonyl compounds, and in fact no evidence of diarylation has been found. But when dimethylhydroxylamine is used, mono-, di-, and tri-arylation should be possible, and the diarylated product should be oxidised to a diaryl ketone (through its oxime). This has been found, and nearly 10% of 4 : 4'-dichlorobenzophenone was isolated (Table 2). This suggests that the low yields of carbonyl compounds in general are in part at least the result of polyarylation. It is not obvious why autoxidation occurs at the unarylated

<sup>7</sup> Beech, *J.*, 1954, 1297.

TABLE 2. Reaction between diazotised amine  $R' \cdot C_6H_4 \cdot NH_2$  and  $Me_2N \cdot OH$ .

R'	Molar ratio $R' \cdot C_6H_4 \cdot NH_2 : Me_2N \cdot OH$	Aldehyde, and yield	Deriv. of aldehyde *	Ketone, and yield	Deriv. of ketone *
H	1	Ph·CHO, b. p. 175—178°, 11%	D, m. p. 227— 228°	Ph <sub>2</sub> CO, 2·4% as deriv.	D, m. p. 236— 237°
H	2	Not isolated	—	Ph <sub>2</sub> CO, 4·7%	D, m. p. 234— 236°
<i>o</i> -Cl	2	<i>o</i> -Cl·C <sub>6</sub> H <sub>4</sub> ·CHO, b. p. 96°/19 mm., 8·5%	D, m. p. 206— 208°	( <i>o</i> -Cl·C <sub>6</sub> H <sub>4</sub> ) <sub>2</sub> CO as deriv. (trace only)	D, m. p. 200— 202°
<i>m</i> -Cl	1	<i>m</i> -Cl·C <sub>6</sub> H <sub>4</sub> ·CHO, b. p. 206—208°, 14%	S, m. p. 229°	( <i>m</i> -Cl·C <sub>6</sub> H <sub>4</sub> ) <sub>2</sub> CO, m. p. 122°, < 5%	D, m. p. 236— 238°
<i>p</i> -Cl	1	<i>p</i> -Cl·C <sub>6</sub> H <sub>4</sub> ·CHO, b. p. 110—113°/ 22 mm., m. p. 47—48°, 35%	S, m. p. 235— 236°; O, m. p. 108—109°	Not isolated	—
<i>p</i> -Cl	2	Not isolated	—	( <i>p</i> -Cl·C <sub>6</sub> H <sub>4</sub> ) <sub>2</sub> CO, m. p. 144— 145°, 8·5%	—
<i>o</i> -NO <sub>2</sub>	2	<i>o</i> -NO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub> ·CHO, m. p. 42—43°, 6%	—	None	—

\* See Table 1.

carbon while arylation, also by a free-radical mechanism, is at the arylated chain. The probable explanation is that both processes are operative in both cases, but manifest themselves oppositely. The diaryl ketones are not easily isolated, and true yields may be higher.

The isolation of diaryl ketones also shows that the mechanism of the reaction differs from that described by Beech: he was unable to effect condensation with aromatic aldoximes. Further, Beech carried out his reaction near neutrality, where hydroxylamines do not condense. It is likely that the alkaline conditions have a deleterious effect on the aldehyde (and oxime) formed in the hydroxylamine reaction, and the neutral conditions are a further point in favour of Beech's process in this case.

Arylation on the nitrogen atom has been studied in less detail as the yields are low and the method held out no promise of being preparatively useful. But in two examples dialkylarylamines, or derivatives from them, were isolated by a modification of the procedure described.

After the preliminary publication<sup>8</sup> of this novel reaction, Brown and Grundy<sup>9</sup> examined the reaction of diazotised 4-aminodiphenyl and diethylhydroxylamine and obtained, not 4-acetyldiphenyl, but the corresponding aldehyde. A mechanism was put forward to explain this surprising result, for which no analogy has been found in the present work and which is not easy to accept. It is not clear why 4-aminodiphenyl should be unique, nor does the proposed mechanism require the concentrated alkali which appears to be essential for reaction. No attempt has been made to repeat this example, but one experiment was made with 4-aminodiphenyl and dipropylhydroxylamine. By the mechanism proposed by Brown and Grundy, the product should have been 4-acetyldiphenyl; unfortunately, no carbonyl compound was isolated, so the problem remains open.

*N,N*-Dibenzylhydroxylamine<sup>10</sup> should react with diazonium compounds in the same way as do the purely aliphatic hydroxylamines, to give mixed diaryl ketones. Unfortunately, this attractive possibility is prevented by the very low solubility of dibenzylhydroxylamine and its salts. Attempts have been made to cause diazonium salts to react with dispersions of the hydroxylamine, but the rate of decomposition of the diazonium salt far exceeded that of condensation, if any.

## EXPERIMENTAL

*General Method for the Preparation of Acylbenzenes.*—The preparations were carried out on 0·25-molar scale. The amine was diazotised by use of the minimum of acid. Hydroxylamine

<sup>8</sup> Rogers, *Chem. and Ind.*, 1953, 1033.<sup>9</sup> Brown and Grundy, *ibid.*, 1954, 460.<sup>10</sup> Behrend and Leuchs, *Annalen*, 1890, 257, 216.

hydrochloride (0.275 mole) was added, and the mixture run in with vigorous stirring, during 15–20 min., to 2*N*-sodium hydroxide (500 c.c.), at <10° (cooling). To the mixture was added a solution of hydrated copper sulphate (1 g.) in water (100 c.c.) and, still with stirring, air was blown through for several hours until the mixture no longer reduced triphenyltetrazolium chloride.<sup>11</sup> The solution, neutralised with concentrated hydrochloric acid and treated with ferric alum<sup>7</sup> (350 g.), was heated under reflux for 5–6 hr., acidified, and distilled in steam. The acylbenzene, containing some hydrocarbon derived from the amine, and some azo-compound, was isolated from the distillate with ether. All preparations were coloured yellow to orange-brown by azo-compound unless the ketone was purified, after the distillation in steam, through the Girard complex. The recorded b. p.s show the limits of the temperature range; the bulk of the material collected boiled over a shorter range.

However, crude *o*-nitroacetophenone was converted directly into its 2:4-dinitrophenylhydrazone, and crude *p*-nitroaceto- and propio-phenone were purified through the Girard P complex.

The condensations with dimethylhydroxylamine were carried out with either a 1:1 or a 2:1 ratio of diazo-compound to hydroxylamine, the latter being intended to favour benzophenone formation (cf. Table 2, in which yields are based on the aromatic amine). In the latter case a positive diazo-reaction usually persisted for several hours. A rough separation of aldehyde and ketone could be effected in some cases by virtue of the much lower steam-volatility of the ketone. Alternatively, the aldehyde was isolated through its bisulphite compound. Dimethylhydroxylamine cannot conveniently be stored except as the oxalate; the required amount, in water, was treated with 1 mol. of hydrochloric acid, and the oxalic acid removed by filtration. This solution was used for admixture with the diazonium salt.

4: 4'-Dichloroazobenzene from the Products of Condensation of *p*-Chlorobenzenediazonium Chloride and Dipropylhydroxylamine.—The diazonium salt (0.5 mole) was run into a mixture of the hydroxylamine and aqueous sodium hydroxide in the presence of copper sulphate (50 c.c. of a 5% solution of hydrate). From the residue of the distillation of the *p*-chloroacetophenone, by extraction of the rather tarry solid with hot methanol, the orange azo-compound was obtained, having m. p. and mixed m. p. 180–181° (from light petroleum). In no experiment was diphenyl or a substituted diphenyl isolated.

Acetophenone Oxime and Phenol from Benzenediazonium Chloride and Diethylhydroxylamine.—Condensation was carried out under the standard conditions, followed by autoxidation with copper as catalyst for 2 hr. The mixture was adjusted to neutrality by 2*N*-hydrochloric acid and steam-distilled (500 c.c.). During much of this the distillate, which was alkaline to Brilliant-yellow paper, did not reduce triphenyltetrazolium chloride, but did when acidified and warmed. The total distillate was extracted with ether, and the extract was dried (K<sub>2</sub>CO<sub>3</sub>, then NaOH pellets). A bulky precipitate of platelets began to separate as soon as the latter was added. The mixture was kept for 24 hr with occasional shaking and the hygroscopic precipitate collected by decantation from residual sodium hydroxide, and dissolved in a little water. The clear solution was extracted with ether, and the combined extracts washed with 0.5*N*-sodium hydroxide, dried, and concentrated to give acetophenone oxime (1.0 g.), m. p. and mixed m. p. 58–60° (from light petroleum). No attempt was made to make the isolation quantitative. The aqueous sodium hydroxide layer was neutralised and phenol isolated as its tribromo-derivative, m. p. 90–91°.

Benzophenone Oxime from Benzenediazonium Chloride and Dimethylhydroxylamine.—To dimethylhydroxylamine oxalate (38 g., 0.25 mole) in 8*N*-sodium hydroxide (500 c.c.) was added hydrated copper sulphate (2.5 g.) in a little water, and the mixture was cooled below 15° with stirring. Benzenediazonium chloride (from aniline, 46.5 g., 0.5 mole) was run in, during about ½ hr., and air was blown through the mixture for a further 2 hr. The solution was acidified with concentrated hydrochloric acid and extracted with ether; the extract was dried and the solvent evaporated. The residual brown oil was lixiviated with hot light petroleum (b. p. 40–60°), and the extract boiled with charcoal, filtered, and evaporated, to give a mixture of oil and solid. The solid was washed carefully with ice-cold cyclohexane and left benzophenone oxime, needles, m. p. and mixed m. p. 137–139° (1.2 g.), autoxidised characteristically in air to nitric acid and benzophenone.

Diethylaniline and Acetophenone Oxime from Benzenediazonium Chloride and Diethylhydroxylamine.—The diazo-compound (0.25 mole) was run into a mixture of diethylhydroxylamine (0.25 mole) and 2*N*-sodium hydroxide (500 c.c.) at <18°. The solution was acidified and distilled

<sup>11</sup> Rogers, *J.*, 1955, 769.

in steam and the combined residues from four such experiments were made alkaline and distilled in steam. The ether-extract of the distillate left on evaporation an oil (28.7 g.): this was fractionated (8" × ½" packed column) at 16 mm. to give (i) diethylaniline, b. p. 90.5—108° (4.9 g.), identified as its picrate (m. p. and mixed m. p.), and (ii) acetophenone oxime, b. p. 108—109° (6.9 g.)

*p*-Chlorobenzaldehyde, 4 : 4'-Dichlorobenzophenone, and *p*-Chloro-*NN*-dimethylaniline from *p*-Chlorobenzenediazonium Chloride and Dimethylhydroxylamine.—Diazotised *p*-chloroaniline (0.1 mole) solution was run into a mixture of dimethylhydroxylamine (0.2 mole) and *N*-sodium hydroxide (50 c.c.), further sodium hydroxide being added to keep the solution alkaline. Acidification (concentrated hydrochloric acid) and distillation in steam gave *p*-chlorobenzaldehyde; and from the dark solid in the aqueous residue 4 : 4'-dichlorobenzophenone, m. p. 143—144°, was isolated by crystallisation from alcohol. The aqueous layer was then made strongly alkaline and again distilled in steam. The ether-extract of the distillate was dried (K<sub>2</sub>CO<sub>3</sub>) and concentrated, leaving a brown oil (1.33 g.) which yielded the 1 : 3 : 5-trinitrobenzene complex, m. p. and mixed m. p. 120—121°, of *p*-chloro-*NN*-dimethylaniline.

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