[COMMUNICATION NO. 1238 FROM THE KODAK RESEARCH LABORATORIES]

Indoaniline Dyes. III. Coupling of para-Substituted Phenols with Oxidized *p*-Aminodimethylaniline

BY PAUL W. VITTUM AND GORDON H. BROWN

In earlier papers in this series[1] we have described the formation of indoaniline dyes by coupling of oxidized *p*-aminodimethylaniline with substituted phenols. Most of the phenols studied had substituents located ortho or meta to the phenolic hydroxyl group, leaving the para-position free for the dye-forming reaction.

So far as we know, the ability of para-substituted phenols to couple with oxidized *p*-phenylenediamines to form indoaniline dyes has not been studied systematically. An early German patent[2] assigns an *o*-quinonimide structure to the dye formed from *p*-aminodimethylaniline and *p*-chlorophenol, but this formulation is made highly questionable by later publications. Thus, it has been established that the coupling reaction with 2,4-dichloro-1-naphthol involves replacement of the 4-chloro atom and formation of a *p*-quinonimide dye.[3] Moreover, numerous recent patents[4] relating to photographic color development have indicated that phenols having para-halogen, sulfonic acid or carboxylic acid groups undergo the coupling reaction by replacement of the para-group. In the second paper of this series,[1b] two *p*-chlorophenol derivatives were shown to lose chlorine on coupling, and a related reaction between oxidized aminoantipyrine and certain para-substituted phenols has been postulated[5] as occurring by replacement of the para-groups.

In the present work, the oxidative condensation of *p*-aminodimethylaniline with a wider variety of para-substituted phenols has been examined. Our object was to ascertain which para-substituents permitted the coupling reaction to occur, and to establish whether the reaction, when it did take place, involved replacement of the para-group or coupling in the ortho-position. The latter question has particular interest because *o*-indoaniline dyes represent a class of compounds about which little is known. Hodgson and Nicholson have reported[6] the formation of such ortho-dyes in certain nitroso condensation reactions, but the dyes were not isolated, their structures being deduced solely from their red color in cold concentrated sulfuric acid. It has also been suggested[7] that *o*-indoaniline dyes are formed from *p*-aminodialkylanilines and urethan derivatives of J acid.[8]

Use was made of the preparative method described previously,[1a] in which the *p*-aminodimethylaniline is oxidized with silver chloride in an alkaline solution containing the phenolic coupler. Under these conditions, no indication of dye formation could be observed with the phenols listed in Table I. The para-substituents in these phenols apparently cannot be expelled by the oxidized *p*-aminodimethylaniline. It is noteworthy that none of this group of para-substituted phenols showed any tendency to undergo coupling in the ortho-position. The activation of the ortho-position in these phenols must be insufficient to permit the coupling reaction to occur before other decomposition reactions of the rather unstable semiquinone intermediate[1a] take place.

TABLE I

para-SUBSTITUTED PHENOLS SHOWING LITTLE OR NO COUPLING REACTIVITY

para-Group	Phenol
R	*p*-Cresol
	3,4-Dimethylphenol
	p-*t*-Butylphenol
	p-Benzylphenol
	p-Hydroxydiphenyl
—CH_2CO_2H	*p*-Hydroxyphenylacetic acid
—CHO	*p*-Hydroxybenzaldehyde
—COR	*p*-Hydroxypropiophenone
	p-Hydroxybenzophenone
—CO_2R	Ethyl *p*-hydroxybenzoate
	Propyl *p*-hydroxybenzoate
—NHCOR	Acetyl-*p*-aminophenol
—N_2R	*p*-Hydroxyazobenzene
—OH	Hydroquinone
—AsO_3H_2	*p*-Hydroxyphenylarsonic acid

Within another group of para-substituted phenols, listed in Table II, coupling reactivity was observed in varying degrees. With some of these phenols, dye formation could be seen to occur rapidly at the start of the reaction, and in these cases the reaction proceeded normally and the dye could be isolated without difficulty. Some of the phenols, however, reacted noticeably

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(1) (a) THIS JOURNAL, **68**, 2235 (1946); (b) **69**, 152 (1947).

(2) German Patent 158,091, cited in "Beilstein" (4th ed.), Vol. 13, J. Springer, Berlin, 1933, p. 88.

(3) Porai-Koshits, *Bull. Acad. Sci. U. R. S. S., Classe sci. chim.*, No. 3, 261–270 (1945); see, also, Flannery and Collins, *Phot. J.*, **86B**, 86 (1946).

(4) See, for example, the following U. S. Patents: Kirby, 2,330,291 (1943); Salminen, Vittum and Weissberger, 2,367,531 (1945); Vittum and Peterson, 2,369,929 (1945); Jennings, 2,395,484 (1946); Bavley, 2,418,747 (1947); McQueen, 2,423,460 (1947); Salminen and Weissberger, 2,423,730 (1947); Bavley, 2,425,503 (1947); Kendall and Fry, 2,441,491 (1948).

(5) Emerson, Kelly, Beacham and Beegle, *J. Org. Chem.*, **9**, 226 (1944).

(6) Hodgson and Nicholson, *J. Chem. Soc.*, 1405 (1939).

(7) Tulagin, U. S. Patent 2,445,252 (1948).

(8) Experiments in these Laboratories, to be described in a future publication, have shown that β-naphthol derivatives undergo oxidative condensation with *p*-aminodialkylanilines to give *o*-indoaniline dyes which are, however, rapidly converted by ring closure to more complex structures.

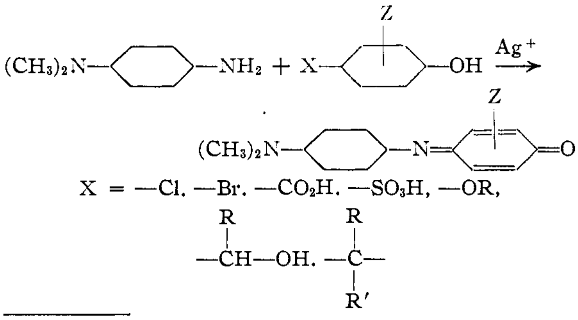
TABLE II

INDOANILINE DYES FROM *para*-SUBSTITUTED PHENOLS

para-Substituent	Coupler used	Procedure	M. p., °C.[a]	% Yield	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Absorption in methanol $\lambda_{max.}$, Å.	Absorption in methanol $\epsilon_{max.} \times 10^{-3}$
—Cl	*p*-Chlorophenol	2	161–162[b]	31	74.3	74.0	6.2	6.2	12.4	12.3	6100[b]	23.4[b]
	2-Methyl-4-chlorophenol	1	124–125[c]	75	75.0	74.9	6.7	7.0	11.7	11.5	6000[c]	20.0[c]
	3-Methyl-4-chlorophenol	2	122–123[d]	80	75.0	74.6	6.7	6.9	11.7	11.6	6070[d]	18.4[d]
	2,4-Dichlorophenol	2	124–125 (dec.)[e]	25	64.5	64.2	5.0	5.1	10.8	10.7	6350[e]	28.0[e]
—Br	*p*-Bromophenol	2	162–163[b]	10	74.3	74.0	6.2	5.8	12.4	12.2	6100[b]	23.3[b]
$—CO_2H$	*p*-Hydroxybenzoic acid	2	162–163[b]	25	74.3	73.9	6.2	5.9	12.4	12.4	6100[b]	23.4[b]
$—SO_3Na$	Sodium *p*-phenolsulfonate	3	162–163[b]	10	74.3	74.4	6.2	6.0	12.4	12.2	6100[b]	23.6[b]
—OR	Hydroquinone monomethyl ether	1	162–163[b]	39	74.3	74.8	6.2	6.4	12.4	12.2	6100[b]	23.7[b]
	Hydroquinone monobenzyl ether	1	162–163[b]	30	74.3	74.5	6.2	6.4	12.4	12.4	6100[b]	23.7[b]
	Vanillyl alcohol	1	168–169[f]	28	70.3	70.6	6.3	6.2	10.9	11.2	6000[f]	18.0[f]
—RCH—OH	*p*-Hydroxybenzohydrol	1	162–163[b]	40	74.3	74.1	6.2	6.1	12.4	12.6	6100[b]	23.5[b]
	p,*p*′-Dihydroxydiphenylmethane	2	161–162[b]	23	74.3	74.1	6.2	6.4	12.4	12.5	6100[b]	23.4[b]
—RCR′—	2,2-Di-(*p*-hydroxyphenyl)-propane	2	162–163[b]	34	74.3	74.7	6.2	6.4	12.4	12.4	6100[b]	23.5[b]
	2,2-Di-(4′-hydroxy-3′-methylphenyl)-propane	2	124–125[c]	33	75.0	74.6	6.7	6.8	11.7	11.7	6000[c]	20.0[c]

[a] Melting points are uncorrected. [b] Previously reported[1a] as the dye made from phenol: m. p., 161–162°; $\lambda_{max.}$, 6100 Å.; $\epsilon_{max.}$, 23.5 × 10³. [c] Previously reported[1a] as the dye made from *o*-cresol: m. p., 123–124°; $\lambda_{max.}$, 6000 Å.; $\epsilon_{max.}$, 19.6 × 10³. [d] Previously reported[1a] as the dye made from *m*-cresol: m. p., 118–119°; $\lambda_{max.}$, 6070 Å.; $\epsilon_{max.}$, 18.3 × 10³. [e] Previously reported[1a] as the dye made from *o*-chlorophenol: m. p., 125° (dec.); $\lambda_{max.}$, 6350 Å.; $\epsilon_{max.}$, 27.3 × 10³. [f] Previously reported[1a] as the dye made from guaiacol: m. p., 167–168°; $\lambda_{max.}$, 6000 Å.; $\epsilon_{max.}$, 18.5 × 10³.

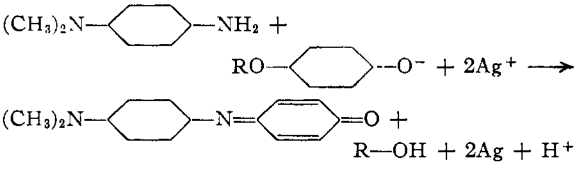
more slowly at the start, and the bright blue color of the dye gradually became degraded as the reaction progressed. When this happened, it was difficult to isolate any pure dye from the reaction mixture.[9] It was found that much better dye formation could be obtained with these sluggish couplers by changing the conditions so that an excess of the coupler was used instead of the usual excess of *p*-aminodimethylaniline. By the proper choice of reaction conditions, it was possible to prepare the indoaniline dyes in pure form from all of the phenols listed in Table II. Identification of the dyes (by analysis and determination of physical and absorption properties) showed that *all of the phenols having coupling reactivity couple by elimination of the substituent* para *to the —OH group* according to the reaction scheme



$$X = —Cl, —Br, —CO_2H, —SO_3H, —OR, —\overset{R}{\underset{}{C}}H—OH, —\overset{R}{\underset{R'}{C}}—$$

This behavior on the part of *p*-hydroxybenzoic acid is not surprising, since it is known that the carboxyl group in this compound is rather easily eliminated in other reactions, for example, with bromine in sodium hydroxide solution,[10] with nitric acid,[11] or with diazonium compounds.[12,13] Similarly, phenol-*p*-sulfonic acid is known[13] to lose its sulfonic acid group in coupling with diazonium compounds.

Analogies can also be found for the other para-substituted phenols which yield indoaniline dyes by elimination coupling. The *p*-alkoxyphenols, for example, react according to the scheme



In effect, this reaction transforms the alkoxyphenol ring into a quinoid structure, and hence might be viewed as similar to the oxidation of *p*-alkoxyphenols to quinone which has been reported to be effected by heating with silver solutions[14] or with nitric acid.[15] The analogy fails, however, in that hydroquinone, which is still

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[9] More recent experiments, to be described in a later paper of this series, have led to the separation and identification of some of the by-products formed in these coupling reactions.

[10] Hähle, *Frdl.*, **3**, 846 (1891).

[11] Diepolder, *Ber.*, **29**, 1756 (1896).

[12] Grandmougin and Freimann, *Ber.*, **40**, 3454 (1907).

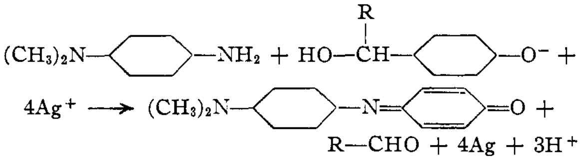
[13] Hickinbottom, "Reactions of Organic Compounds," 2nd ed., Longmans, Green and Co., London, 1948, p. 121.

[14] Hlasiwetz and Habermann, *Ann.*, **177**, 341 (1875).

[15] Kauffmann and Fritz, *Ber.*, **43**, 1215 (1910).

more easily oxidized to quinone, fails to undergo coupling to produce an indoaniline dye.

The elimination coupling of the *p*-hydroxyphenyl carbinols follows the reaction



which may be compared with the splitting of the carbinols by bromine.[16] Similarly, an analogy may be drawn between the coupling of the alkylidene-bis-phenols and the diazo coupling of 2,2′-dihydroxy-1,1′-dinaphthylmethane which splits and yields the same azo dye formed from β-naphthol.[17]

The yields of indoaniline dyes given in Table II may be taken as roughly indicative of the reactivities of the different *para*-substituted phenols in the coupling reaction. The yields are not, of course, a direct measure of reactivities throughout the group since different conditions were employed in some of the reactions. The *p*-chloro compounds illustrate the important point that additional substituents have a strong influence on the coupling reactivity, a positive group such as $—CH_3$ greatly increasing the reactivity whereas a second —Cl reduces it. Additional substituents in the inactive compounds of Table I might be expected to make them more reactive and, in fact, it has been shown,[18] for example, that certain 4-phenylazo derivatives of α-naphthol and substituted phenols do undergo indoaniline coupling, with elimination of the phenylazo group.

Experimental[19]

Except for the phenols described below, the organic reactants and solvents used in preparing the dyes were Eastman Kodak Company chemicals, white label grade if available, otherwise practical grade. Inorganic chemicals of reagent grade were employed. 2-Methyl-4-chlorophenol was obtained from the Dow Chemical Company.

***p*-Hydroxybenzhydrol.**—This was prepared by reduction of *p*-hydroxybenzophenone with sodium amalgam, according to the procedure of Döbner.[20] The material was obtained in 48% yield, melting at 161–162°, after one crystallization from 50% ethanol.

***p*,*p*′-Dihydroxydiphenylmethane.**—*p*,*p*′-Diaminodiphenylmethane in hot acid solution was treated with sodium nitrite. following the procedure of Staedel.[21] The product, obtained in 45% yield, consisted of glistening white plates, melting at 149°.

2,2-Di-(*p*-hydroxyphenyl)-propane.—Phenol and acetone were condensed by means of hydrochloric acid, following the general procedure outlined by Reid and Wilson.[22] The best results were obtained by mixing 11.6 g. (0.2 mole) of acetone, 56.4 g. (0.6 mole) of phenol, and 12 cc. of concentrated hydrochloric acid, and saturating the mixture with dry hydrogen chloride gas once a day over a period of a week. The solid reaction mixture was broken up in water and the excess phenol was removed by steam-distillation. The nearly white, non-oily solid was filtered off and dried, then recrystallized from toluene, yielding 41 g. (90%) of white needles, melting at 151°.

2,2-Di-(4′-hydroxy-3′-methylphenyl)-propane.—This was prepared in the same manner, starting with *o*-cresol and acetone. The product was recrystallized from carbon tetrachloride, giving a 69% yield of fine white crystals, melting at 138–140°.

Preparation of Dyes.—Three procedures were used, the choice depending upon the reactivity of the particular coupler. **Procedure 1**, which was identical with that described previously,[1a] was preferable for the more reactive couplers since it gave a crude product which was free from excess coupler and hence easier to purify. **Procedure 2** differed in that 0.025 mole of *p*-aminodimethylaniline hydrochloride and 0.05 mole of the phenol were employed. At the completion of the reaction, the mixture was stirred with ether and filtered, and the separated ether layer was washed with four 100-cc. portions of 1% sodium hydroxide solution to remove unreacted phenol, then with four portions of water. **Procedure 3** was worked out specifically for *p*-phenolsulfonic acid which failed to give a pure dye by either of the other procedures. The best results were obtained by using 0.075 mole of *p*-phenolsulfonic acid and 0.025 mole of *p*-aminodimethylaniline hydrochloride. The reaction was carried out in a two-phase system with ethyl acetate as the non-aqueous phase. The aqueous phase was adjusted to a *p*H of 9.0 and then the *p*-phenylenediamine was added very rapidly. No other set of conditions was found which gave a crude dye capable of being brought to analytical purity.

All the dyes were crystallized twice from ligroin, b. p., 90–120°, and, finally, once from absolute ethanol.

Isolation of Other Reaction Products.—The coupling reactions with hydroquinone monobenzyl ether and *p*-hydroxybenzohydrol were repeated and the reaction mixtures worked up to isolate the reaction products other than the dye. For this purpose, the reactions were run using twice the quantities specified for procedure 1 and the reaction mixture was subjected to steam-distillation. The distillate was acidified with hydrochloric acid and shaken out with ether. The ether layer was dried with anhydrous magnesium sulfate, the ether was evaporated, and the residue distilled under reduced pressure. From hydroquinone monobenzyl ether was obtained 3.1 g. (57%) of benzyl alcohol, identified as the 3,5-dinitrobenzoate, m. p., 109°. Mixing with a known sample, also melting at 109°, gave no lowering of the melting point. *p*-Hydroxybenzohydrol yielded 2.2 g. (41%) of benzaldehyde, identified as the semicarbazone. m. p. 223°, alone and mixed with a known sample.

Spectrophotometric Measurements.—The dyes were dissolved in specially purified methanol to make 6.5×10^{-5} *M* solutions which were read in 1-cm. cells, using the General Electric Automatic Recording Spectrophotometer.

Acknowledgment.—The authors are grateful to Mr. E. E. Richardson, of these Laboratories, for supplying the methanol and making all of the spectrophotometric measurements.

Summary

The coupling reaction between oxidized *p*-aminodimethylaniline and para-substituted phenols has been investigated. Many of the phenols failed to react to produce an indoaniline dye. Phenols bearing para-halogen, $—CO_2H$, $—SO_3H$, —OR, —RCH—OH, or —RCR′—groups, on the other hand, were found to react more or

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[16] Kohler and Patch, This Journal, **38**, 1205 (1916).

[17] Möhlau and Strohbach, *Ber.*, **33**, 804 (1900); **34**, 4162 (1901).

[18] Glass, Vittum and Weissberger, U. S. Patent 2,455,169 (1948).

[19] Some of the early experimental work on this problem was done by Mrs. Gretchen Stewart, whose assistance is here gratefully acknowledged.

[20] Döbner, *Ann.*, **210**, 253 (1881).

[21] Staedel, *ibid.*, **283**, 163 (1894).

[22] Reid and Wilson, This Journal, **66**, 967 (1944).

less readily to yield *p*-indoaniline dyes by elimination of the para-substituent. The ease with which the elimination coupling occurred appeared to be influenced by the presence of other substituents in the phenol ring. No evidences of *o*-indoaniline dye formation were observed with any of the phenols studied.

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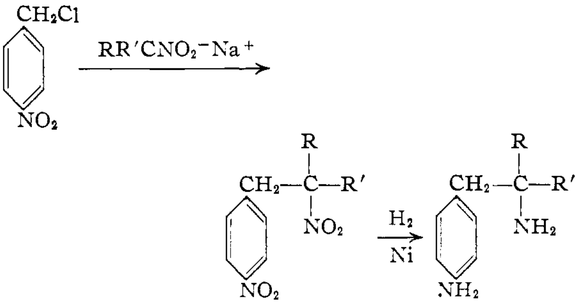
Carbon Aralkylations of Nitro Paraffins[1]

BY H. B. HASS, E. JANET BERRY[2] AND MYRON L. BENDER[3]

The isolation of adrenalin and discovery of its physiological activity led to an intensive search for synthetic substitutes in the β-phenethylamine series. In this series correlations have been found between structure and sympathomimetic activity. *t*-Carbinamines R_3CNH_2 are of particular importance as sympathomimetic drugs because they cannot be deaminated in the body by the usual mechanism involving oxidation to the imine and subsequent hydrolysis.

There have been many investigations of the synthesis of *t*-carbinamines.[4] One approach to their synthesis is the alkylation of nitro paraffin salts followed by reduction of the nitro compound produced. Weisler[5] made an extensive review of the literature on the alkylation of nitro paraffin salts, which showed that, in general, oxygen-alkylation products, oximes and carbonyl compounds, are formed. However, it was indicated by the work of Dunning[6] and Hoover[7] that alkylation of nitro paraffin salts with *p*-nitrobenzyl chloride results in carbon-alkylation (a new carbon–carbon bond).

A series of seven nitro paraffin salts has been treated with *p*-nitrobenzyl chloride, forming carbon-alkylation products in every case. No effort was made to isolate products of oxygen-alkylation. The products, dinitro compounds, were then reduced to the corresponding diamines. The over-all scheme is shown in Fig. 1.



R and R' = H. alkyl. or cycloalkyl

Fig. 1.

The dinitro compounds and diamines prepared in this manner, together with their physical constants and analyses, are summarized in Tables I and II. The experimental procedures for only one alkylation and one reduction are described in the experimental section. They are, however, representative of the methods used in all the alkylations and reductions.

Experimental[8]

Materials.—Nitroethane (n^{20}_D 1.3915), 1-nitropropane (n^{20}_D 1.4013), 2-nitropropane (n^{20}_D 1.3940), 1-nitrobutane (n^{20}_D 1.4110), and 2-nitrobutane (n^{22}_D 1.4037) were rerectified Commercial Solvents Corporation products. Nitrocyclohexane was a re-rectified du Pont product. Nitrocyclopentane was prepared according to the directions of Shechter.[9] *p*-Nitrobenzyl chloride was an Eastman Kodak Company product.

Preparation of 2-Nitro-1-(*p*-nitrophenyl)-butane.—Sodium (3.4 g., 0.15 mole) was dissolved in 300 ml. of ethanol. Freshly distilled 1-nitropropane (65 g., 0.73 mole)[10] and then *p*-nitrobenzyl chloride (25 g., 0.15 mole) were added. After refluxing for eight hours,[11] the mixture was filtered to remove the sodium chloride. The filtrate was evaporated to a yellow oil. This oily residue formed a yellow solid after cooling and stirring with a small amount of ethanol. Recrystallization from ethanol gave 16.5 g. of 2-nitro-1-(*p*-nitrophenyl)-butane; yield 50.6%; m. p. 64–65°.

Preparation of 1-(*p*-Aminophenyl)-2-butylamine.—2-Nitro-1-(*p*-nitrophenyl)-butane (16.5 g., 0.074 mole), 5 g. of Raney nickel, and 300 ml. of ethanol were placed in a hydrogenation bomb. The reaction mixture was subjected to hydrogen at 1200 p. s. i. and 60–70° for eight hours. The catalyst was filtered from the reaction mixture, ethanol was removed under reduced pressure, and the residue was distilled. Nine grams of 1-(*p*-aminophenyl)-2-butylamine was obtained; b. p. 110° (1 mm.); n^{20}_D 1.5642; yield 74.4%.

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[1] Based on a thesis by E. Janet Berry, submitted to the Faculty of Purdue University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1946.

[2] du Pont Fellow, 1944–1946; present address: Standard Oil Development Company, New York, N. Y.

[3] E. K. Lilly Fellow, 1947, American Cyanamid Company Fellow, 1947–1948; present address: Harvard University, Cambridge, Massachusetts.

[4] See Ritter and Kalish, THIS JOURNAL, **70**, 4048 (1948), for a list of references.

[5] Weisler, Doctoral Thesis, University of Rochester, 1939.

[6] Dunning, reported by Weisler, reference 5.

[7] Hoover, Doctoral Thesis, Purdue University, 1941.

[8] All melting points are corrected; microanalyses by Miss Theta Spoor, University of Illinois, Urbana, Illinois, and Mr. H. Galbraith and Miss L. Roth of Purdue University.

[9] Shechter, Doctoral Thesis, Purdue University, 1946.

[10] Since a primary nitro paraffin contains more than one replaceable hydrogen, a 500% excess of the nitro alkane was used in such cases to diminish the formation of polyalkylated products. When a secondary nitro paraffin was used, a 10% excess of the nitro alkane was usually employed.

[11] The condensation using nitrocyclopentane was heated to reflux and then cooled since further heating produced tars.