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An historical review of the use of dye precursors in the formulation of commercial oxidation hair dyes

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Abstract

The changing palette of precursor used in commercial oxidation hair dyes over the period 1900 to 1997 is reviewed. Reasons for changes in the palette are discussed in the light of regulatory and patent activity together with comment on the changes in the paradigm for patentability of combinations of known ingredients in known generic combination.

Keywords: Oxidation; Hair dyes; Commercial use; Patent; Regulation

1. Introduction

Previous reviews of the oxidation hair dye literature have been encyclopedic and offer little insight into which of the thousands of proposed compounds have actually been used in commercial products [1–3]. On the other hand, the technical literature [4–7] has been devoted to elucidating the role the various types of ingredients play in the final formulation, but provides little information on which ingredients have been used commercially, and how and why they have changed over the 100 year history of oxidation dyeing.

The present article attempts to trace the evolution of the palette of dyes and the reasons behind the changes that have occurred, particularly during the last 30 years.

2. The era of pragmatic discovery

Oxidation dyeing of human hair has been practiced for over 100 years and evolved out of an observation that the colorless *p*-phenylenediamine produced a colored compound when subjected to oxidation, and that this reaction could be used to color a variety of substrates.

According to a 1967 review of hair dye patents by Charle and Sag [1], the first patent relating to oxidation dyeing of human hair was applied for in 1883 by Monnet (F.P. 158,558) and disclosed the use of *p*-phenylenediamine or 2,5-diaminotoluene with an oxidizing agent.

Between 1888 and 1897, Hugo and Ernst Erdmann extended the scope of ingredients to include, among others, such precursors as *p*-aminophenol, its *N*-alkyl and 2- and 3-methyl derivatives, *N*-alkyl and *N*-phenyl-*p*-phenylenediamines, 4,4′-diaminodiphenylamine and 1,5-diamino and 1,5-dihydroxynaphthalene. Their patents are also noteworthy in introducing the use of hydrogen peroxide as the oxidant in the dyeing process.

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Covering the period up to 1930, the Charle and Sag paper reviews a further 79 patents, mostly issued to German textile dyestuff manufacturing companies, which enumerate a wide variety of compounds which are now known to be primary intermediates (also referred to as developers or bases) or couplers (or modifiers). The primary intermediates are generally para-diamines or para-aminophenols and, occasionally their ortho isomers. These materials produce colored products on oxidation. The couplers do not produce significant color when oxidized alone, but when present during the oxidation of a primary intermediate can greatly modify the resulting color. These couplers are generally meta-diamines, meta-aminophenols and mono or polyhydric phenols. Those materials listed by Charle and Sag which have been extensively used in commercial products are shown in Table 1. The intermediates listed as "other oxidizeable species" were once considered as "primary intermediates"; however, it is unlikely that they behave as such, since they are very readily oxidized and undergo different types of reaction.

It is interesting to note that none of these early dyestuff patents were granted to the major hair dye companies in the business today, even though many of them were founded prior to 1930.

Charle and Sag observed that when nitro dyes, such as 2-amino-5-nitrophenol, 3-nitro-4-aminophenol, 4-nitro-*o*- and 4-nitro-*m*-phenylenediamine, were patented for use in oxidation dyes in 1898, "the inventors did not recognize their departure from the oxidation base type of product". It was later recognized [2,4] that these materials did not participate in the oxidative coupling reactions, but acted as direct dyes. These dyes were used extensively in shades requiring yellow or red nuances.

In 1934, when Lawrence Gelb purchased formulae from Dr. Friedrich Klein in Germany and used them as the basis for founding the Clairol Company in the United States, his notebooks show a line of shades based on eight colorless precursors and two direct dyes (Table 2). All but one of these ingredients, 4-chlororesorcinol, are listed in Table 1.

Klein's formulae give an indication of the role played by the various intermediates, as can be seen from the shade breakdown of Clairol's early products in Table 2. Clearly, the drab shades relied heavily on para-diamines, meta-diamines and resorcinols, while the combination of *p*-aminophenol with meta-diamines and 4-nitro-*o*-phenylenediamine was important to the formulation of warm shades.

Table 3 shows the palettes used during the period 1934–1971. The list contains 20 colorless precursors and six direct dyes, of which 12 of the colorless precursors and three of the direct dyes are still used extensively. From these data, it is clear that a basic palette for a line of shades comprised one or more para-diamines, together with meta-diamines, resorcinols, and *o*- and *p*-aminophenols,

Table 1
Dye intermediates of commercial importance which were patented between 1883 and 1930

Primary intermediates	Couplers
p-Phenylenediamine	*m*-Phenylenediamine
2,5-Diaminotoluene	2,4-Diaminoanisole
N-Phenyl-*p*-phenylenediamine	2,4-Diaminophenetole
2-Chloro-*p*-phenylenediamine	
2-Methoxy-*p*-phenylenediamine	1,5,-Dihydroxynaphthalene
N,*N*-Dimethyl-*p*-phenylenediamine	
o-Phenylenediamine	2,7-Dihydroxynaphthalene
p-Aminophenol	Resorcinol
3-Chloro-4-aminophenol	
5-Chloro-2-aminophenol	*Other oxidiseable species*
N-Methyl-*p*-aminophenol	2,4-Diaminophenol
o-Aminophenol	4,4′-Diaminodiphenylamine
	4,4′-bis(dimethylamino)-diphenylamine

Table 2
Dye components in typical Clairol shades in 1934

	Ash blonde	Drab brown	Warm brown	Dark auburn	Mahogany	Black
2,5-Diaminotoluene	x	x			x	x
p-Phenylenediamine	x	x			x	x
4-Chlororesorcinol	x	x			x	x
4-Aminodiphenylamine	x	x			x	x
2,4-Diaminotoluene	x	x	x	x	x	x
2,4-Diaminoanisole					x	
p-Aminophenol	x	x	x	x	x	x
4-Amino-2-nitrophenol	x	x	x	x	x	x
Resorcinol	x	x	x	x	x	x
4-Nitro-*o*-phenylenediamine			x	x		

Table 3
Palettes used in oxidation dyes between 1934 and 1997

	Clairol 1934–1940	Kass 1956	Tucker 1968	Clairol 1970	Kass 1971	Still used 1997
p-Phenylenediamine	x	x	x	x	x	x
2,5-diaminotoluene	x		x	x	x	x
N-Ph-*p*-phenylenediamine	x	x		x	x	x
4,4′-Diaminodiphenylamine					x	
p-Aminophenol	x	x	x	x	x	x
o-Aminophenol		x	x	x	x	x
2-Amino-4-chlorophenol	x					
m-Aminophenol				x	x	x
m-Phenylenediamine				x	x	x
2,4-diaminotoluene	x			x	x	
2,4-diaminoanisole	x	x	x	x	x	
2,4-diaminodiphenylamine				x		
2,4-diaminophenol	x					
Resorcinol	x	x	x	x	x	x
4-Chlororesorcinol	x					x
Pyrogallol		x	x			x
Hydroquinone			x	x	x	x
2-Nitro-*p*-phenylenediamine		x	x	x	x	x
4-Nitro-*o*-phenylenediamine	x	x	x	x	x	
4-Amino-2-nitrophenol	x		x	x	x	
4-Amino-6-chloro-2-nitrophenol			x			x
Picramic acid	x					x

supplemented with direct yellow and red nitro dyes.

From 1926 until 1960 there was little innovation in precursors used or even patented for use in oxidative dyeing. By 1960 most manufacturers were using a basic palette of about 10–15 ingredients supplemented with a few that were particular favorites of individual formulators.

In the United States, Britain and Japan, *p*-phenylenediamine and *p*-aminophenol were the main primary intermediates while, due to regulatory restrictions on the use of the former dating from 1906 and driven by concern about allergic reactions, French and German manufacturers employed 2,5-diaminotoluene and *p*-aminophenol. Here it should be noted, that 2,5-diaminotoluene

is much less efficient, in terms of intensity of color produced, than *p*-phenylenediamine [8]. On a molar basis, about 50% more 2,5-diaminotoluene is required to achieve a particular depth of color.

While *p*-phenylenediamine and 2,5-diaminotoluene are used for most shades, other para-diamines in Tables 1 and 2 have a more specialized function. 2-Chloro-*p*-phenylenediamine has been found useful in formulating drab blonde and light brown shades, while *N*-phenyl-*p*-phenylenediamine is valuable as an additional para-diamine in black shades. In lighter shades, the latter has the disadvantage of giving colors with poor union between intact and damaged hair, as is encountered in dye-back of previously bleached hair or in dyeing hair in which the distal ends have been subjected to permanent waving.

2-Methoxy-*p*-phenylenediamine was found to be useful in producing deeper colors with meta-diamine couplers as was *N*,*N*-dimethyl-*p*-phenylenediamine.

In virtually all shades, the intense brown to black color produced by *p*-phenylenediamine alone was modulated by the addition of resorcinol which produces a golden (greenish) brown tonality. Thus, in 1968, Tucker [9] stated "the achievement of level dyeing is favored by choosing the dye concentration as high as possible for the desired shade. In oxidation hair dyeing this is especially important in dyeing light shades on bleached hair, using the toners, where the porosity of the hair may vary substantially in different areas of the head. This decrease in depth of shade is accomplished by using resorcinol or other phenolic compounds which cause a lightening of the color, thus allowing higher concentration of dye to be used to obtain the desired shade. A mixture of *p*-phenylenediamine and resorcinol is one of the most important and most widely used combinations in oxidation hair dyeing."

While red shades could be obtained by the use of *p*-aminophenol and a *m*-phenylenediamine, the poor stability [4] of the resulting red *N*-(*p*-hydroxyphenyl)-2-amino-benzoquinonediimine (V; X = O, Y = N) led many formulators to prefer to use the red direct dye 2-nitro-*p*-phenylenediamine for these tones.

Similarly, the gold tones obtained using *o*-aminophenol have poor light stability [4], and the use of 4-nitro-*o*-phenylenediamine, 4-amino-2-nitrophenol or 5-nitro-2-aminophenol, each of which behaves as a direct dye, was preferred by most formulators.

Ash shades and black relied heavily on the use of meta-diamines which, in the presence of para-diamines produce blue to violet–blue tones due to the formation of 2-amino-indamines (V; X = Y = NH). Although *m*-phenylenediamine itself was used, most formulators preferred 2,4-diaminotoluene, which gave a purer blue tone or 2,4-diaminoanisole which, while giving a slightly reddish blue, had the advantage of giving shades of greater stability. Thus, in a 1971 paper on oxidative dye formulation [10], Kass stated: "The writer prefers to use 2,4-diaminoanisole rather than *m*-phenylenediamine or *m*-tolylenediamine (2,4-diaminotoluene). The latter two yield purple shades with *p*-phenylenediamine that are less stable than those produced by 2,4-diaminoanisole." Tucker [4] made a similar observation.

3. The era of understanding

By 1970 the role of the various intermediates and the chemistry of the color forming reactions was well understood to those involved in formulating oxidation dyes [3–6]. Essentially, the first step is the oxidation of a primary intermediate (I, X = O or NH) to produce a benzoquinonediimine or monoimine (II, X = O or NH) which reacts with the nucleophilic couplers (III, Y and Z = O or NH) to give a diphenylamine or leuco dye (IV) which, on further oxidation yields an indo dye (V) (Fig. 1).

The dyes formed form the meta difunctional couplers having no substituents para to either of the functional amino and/or hydroxy groups undergo further reaction to give trinuclear compounds (VI) and, in the case of resorcinol, polynuclear species having a somewhat drab color [5] [6]. In contrast, couplers having a blocking group para to one of the functional groups do not react beyond the brightly colored binuclear indo dye (V) [5,6].

Thus, resorcinol, *m*-aminophenol and *m*-phenylenediamine can be regarded as couplers con-

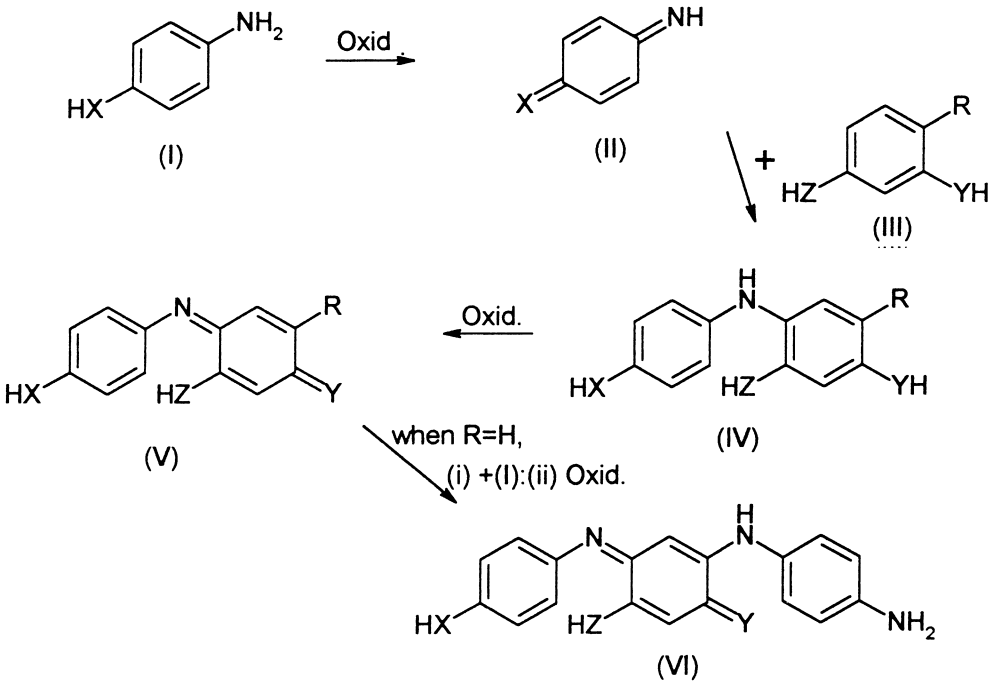


Fig. 1. Dye formation in oxidation dyeing (X,Y, and Z may be independently O or NH).

tributing to the brownish background of the shade while contributing minor greenish, warm and bluish black tones respectively. In contrast, the blocked meta couplers, having a substituent para to one of the functional groups produce intense bright shades when used in conjunction with para-diamines and para-aminophenols. These couplers can be used to give delicate nuances to lighter shades as well as to contribute markedly to the intensity and color of deep shades.

Substituents on the benzene ring of the precursors have a small but significant effect on the color of the resulting indo dye. Thus alkyl and alkoxy groups on the coupler give dyes absorbing at shorter wavelengths i.e. more red, while halogen substitution on the coupler gives dyes absorbing at longer wavelengths i.e. bluer. Analogous substitution of the primary intermediates has the opposite effect on the color [],6]. Thus these precursors form a versatile group of ingredients capable of providing a full range of shades which can be fine-tuned by appropriate modification of the precursors.

4. The era of regulation and reformulation

The evolution of the second generation of oxidation hair dyes began in about 1970 and was driven by two factors. Firstly, from about 1955, major manufacturers had invested heavily in basic research leading to an understanding of the chemistry of the coloring processes and to the synthesis and evaluation of hundreds of novel primary intermediates and couplers. Secondly, there was a recognition that some of the aromatic amines were biologically active and that minute amounts could penetrate through the scalp during the coloring process. Thus, systemic toxicity had to be considered in the safety evaluation of hair dyes.

Although risk assessment techniques indicated that the hypothetical risk to the user was de-minimus, manufactures considered it prudent to avoid continuing adverse publicity that would have been attendant on the continued use of these ingredients. They were thus fortunate that when regulatory concerns arose concerning the safety of some of the important intermediates and direct

dyes used in oxidative hair dyeing, there were viable alternatives at hand.

In 1970, a study in Japan found that tumors were produced when rats were fed high doses of 2,4-diaminotoluene in a protein deficient diet. At the time, the industry had virtually no data on the systemic toxicity of hair dye ingredients since it had been reasonably assumed that the skin was an effective barrier to such exposure. From 1970 to 1980 the US industry, under the coordination of the Cosmetic, Toiletry and Fragrance Association, sponsored extensive testing of hair dye ingredients involving lifetime skin painting studies in rats and mice. Significantly, in these studies, none of the tested materials had any effect on tumor development or reproductive performance. However, since no such data were available in 1970, manufacturers who were using 2,4-diaminotoluene switched to 2,4-diaminoanisole, which latter was already being used by most formulators because of its known superior performance (see above).

In 1972, Clairol introduced products in which *N*,*N*-bis(2-hydroxyethyl)-*p*-phenylenediamine was used as a partial replacement for *p*-phenylenediamine [11]. This new ingredient had the advantages of reduced allergenicity and, when used in conjunction with 2,4-diaminoanisole, it gave a blue aminoindamine that was free of reddish tones, and possessed even greater resistance to fading than the *p*-phenylenediamine/2,4-diaminoanisole couple [7].

Another important innovation of this period was disclosed in a Schwartzkopf patent [12] on a substituted *m*-aminophenol coupler. They found that 5-amino-2-methylphenol (VII; R = H), in contrast to *m*-aminophenol, gave intense brilliant shades when used in conjunction with a primary intermediate. As explained above, this is now understood to occur because the reaction stops at the aminoindophenol (V, X = Y = O, R = CH_3) stage with *p*-aminophenol and the aminoindoaniline (V, X = NH, Y = O, R = CH_3) stage with *p*-phenylenediamine [2]. According to the patent disclosure, the color with para-aminophenols is an intense reddish orange, that with a para-diamine an intense violet, and that with a mixture of para-diamine and *p*-aminophenol is ruby red to burgundy depending on the relative proportions. The inventors further suggested that 2-methyl or 3-methyl-4-aminophenol could be used in place of *p*-aminophenol. For the first time, this made the production of relatively stable red shades, having low pH sensitivity, available without recourse to nitro dyes.

By far the biggest impetus to innovation in formulation followed the publication by Ames et al. in 1975 of his finding that a number of hair dye ingredients were mutagenic in a test which employed modified Salmonella typhimurium. This was soon followed by the findings by the US National Cancer Institute of a carcinogenic effect of some hair dye intermediates in rats and mice in studies in which the maximum tolerated dose of the dye was fed to rats and/or mice.

In the United States in 1979, the Food and Drug Administration, prompted by the positive NCI test on 2,4-diaminoanisole, proposed to require a cancer warning label on hair dyes containing this material. The regulation was stayed in 1980 pending use of "scientific risk assessment" to quantitate the risk. The industry had obtained data on the level of 2,4-diaminoanisole absorbed through the skin during the hair dyeing process and, through conservative risk assessment techniques had shown the maximum hypothetical risk from a lifetime exposure to 2,4-diaminoanisole in hair dyes to be considerably less than one in a million, and less than the similarly calculated risks condoned by FDA in its food regulations e.g. from aflatoxin in peanut butter or pyrolysis products on charcoal broiled steaks. Nevertheless, the industry had already reformulated to eliminate 2,4-diaminoanisole before the case was settled.

The resulting concern, under the prevailing opinion that there was no safe dose for a carcinogen, caused manufactures to reformulate all oxidative dye products during the period 1978–1982. Essentially, this reformulation involved the replacement of 2,4-diaminoanisole as the major blue coupler, and the elimination of some of the red and yellow direct dyes, which had been reported to produce tumors in NCI bioassays.

Ingredient labelling, which was introduced in the United States in 1975 made it possible to follow the changes of formulation, and the post-reformulation palettes of four manufacturers were published in a paper in 1984 [13] and is reproduced here in Table 4.

Clairol [14] chose the combination of *N*,*N*-bis(2-hydroxyethyl)-*p*-phenylenediamine and 1-naphthol to produce blue for its ash shades. Certain tonal families requiring a purer blue tone, employed the 2-equivalent coupler 4,6-bis(β-hydroxyethoxy)-1, 3-diaminobenzene (VIII; $R = HOC_2\ H_4$–) as the blue coupler [15]. They also took a license on the Schwartzkopf patent [12] for use of 5-amino-2-methylphenol in conjunction with *p*-phenylenediamine and *p*-aminophenol, as a means of producing auburn and red shades.

L'Oreal [16] obtained a patent for a novel blue coupler – 2,4-diaminophenoxyethanol (VIII; R = H) which they employed as a replacement for 2,4-diaminoanisole, and another [17] for a variant on Schwartzkopf's material, namely *N*-β-hydroxyethyl-5-amino-2-methylphenol (VII; $R = HOC_2H^{-}{}_4$), which they used in red and auburn shades.

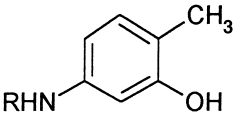
Revlon and a number of other companies initially made the unfortunate choice of 2,4-diaminophenetole as their alternative blue coupler but, after some adverse publicity following FDA's announcement that they had found this material to be positive in the Ames Test, reverted to the use of *m*-phenylenediamine. Additionally, Clairol granted Revlon a sub-license on the use of the Schwartzkopf "red" coupler.

Wella [18] replaced 2,4-diaminoanisole with 2-amino-4-β-hydroxyethylaminoanisole (IX) while Henkel [19] employed 1,3-bis-(2,4-diaminophenoxy)-propane (X) for the same purpose. Wella [20] also introduced the use of 2-amino-5-methylphenol (XI) which self-couples to give a yellow dye (XII). Unlike the parent 2-aminophenol (XIII) which is oxidized to 2-amino-phenoxazin-3-one (XIV), the methyl derivative gives an uncyclized yellow product (Fig. 2).

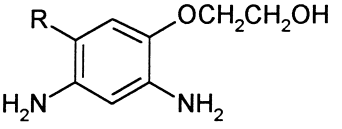
It is interesting to note that the Clairol, L'Oreal, Wella and Henkel meta-diamines mentioned above all contain an alkoxy substituent para to one of the amino groups which is consistent with the preference for 2,4-diaminoanisole mentioned by Kass [10] and Tucker [9].

These changes, together with the introduction in the mid-1980s of the unblocked coupler 2-methylresorcinol, which was found to be valuable in producing a yellow–brown coloration, reduced the industry's reliance on direct dyes and, for the first time complete shade lines based on colorless precursors were available (Table 4). The companies not using 2-methylresorcinol relied on *o*-aminophenol or 2-amino-5-methylphenol (XI) while some continued to use nitro dyes in gold shades.

The ability to make these changes in palette was of vital importance to the industry in the 1980s when the European Union banned the use of a number of previously used ingredients (Table 5), including 2,4-diaminoanisole and several yellow nitro dyes.



(VII)



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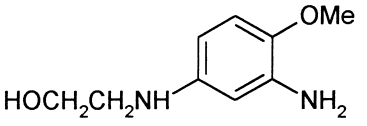

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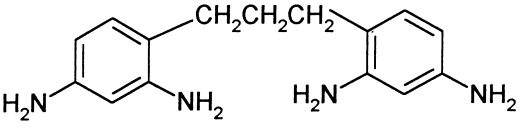

(X)

Table 4
Oxidation dye precursors used by four hair dye manufacturers in the United States in 1984

	Manufacturer				Color with designated primary intermediates
	A	B	C	D	
Primary intermediates					
1. *p*-Phenylenediamine (PPD)	X	X	X	X	
2. 2-Chloro-*p*-phenylenediamine	X	–	X	–	
3. *N*,*N*-bis(2-hydroxyethyl)-PPD	–	–	–	X	
4. *N*-Phenyl-PPD	–	–	X	–	
5. *p*-Aminophenol	X	X	X	X	
6. *o*-Aminophenol	X	–	–	–	
Couplers					
Pyrogallol	X	–	–	–	Brown with 1
Hydroquinone	X	–	–	–	Brown with 1
2,3-Naphthalenediol	X	–	X	–	
Resorcinol	X	X	–	X	Green/Brn with 1 or 2
4-Chlororesorcinol	–	–	X	–	Green/Brn with 1 or 2
2-Methylresorcinol	X	–	–	X	Yellow–green with 1
1-Naphthol	–	–	–	X	Blue with 3
m-Aminophenol	X	X	X	X	Magenta with 1 or 2
5-Amino-2-methylphenol	X	–	–	X	Orange–red with 5
5-Hydroxyethylamino-2-cresol	–	X	–	–	Orange red with 5
m-Phenylenediamine	X	–	–	–	Blue with 1 or 2
2,4-Diaminophenoxyethanol	–	X	–	–	Blue with 1
2,4-Diaminophenetole	–	–	X	–	Blue with 1 or 2
N-Phenylethylpyrazolone	–	X	–	–	Magenta with 1
Direct dyes					*Color*
4-Nitro-*o*-phenylenediamine (NOPD)	–	–	X	–	Yellow
N′-(2-Hydroxyethyl)-NOPD	–	–	X	–	Orange–yellow

A: Revlon; B:L'Oreal; C: Jhirmack; D: Clairol.

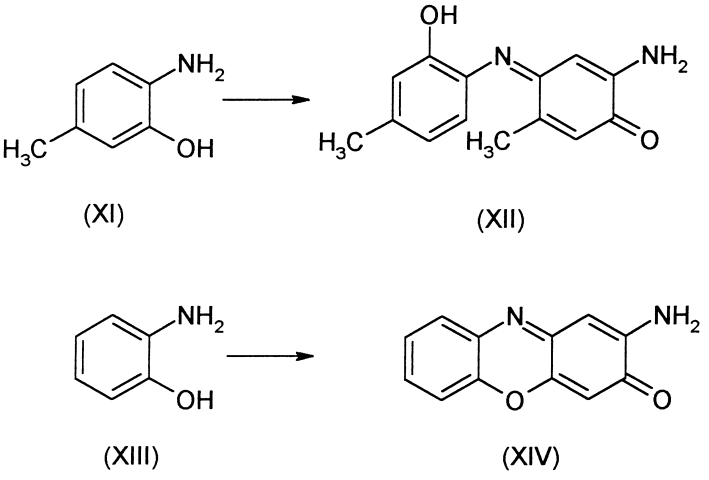

Fig. 2. Oxidation of o-Aminophenols.

Table 5
Ingredients not permitted in hair dye products in the European Union

o-Phenylenediamine
2,4-Diaminotoluene
2,4-Diaminoanisole
2,4-Diaminophenetole
2,4-Diaminophenylethanol
2,5-Diaminoanisole
2-Amino-4-nitrophenol
2-Amino-5-nitrophenol
4-Amino-2-nitrophenol
Catechol
Pyrogallol

5. The era of anticipatory patents

The fifteen years of reformulation which began in 1970 taught the industry that the focus on toxicology could bring major commercial disruptions. By 1976, manufacturers had begun to cooperate in performing batteries of tests on common ingredients and worked individually on the testing of potential alternatives from among the thousands that had been suggested in the literature. In Europe, this activity involved submitting dossiers on the ingredients to the authorities for evaluation by the Scientific Committee on Cosmetics.

The intent was to provide a basic palette of approved ingredients that would be available to the whole industry, while leaving individual companies free to develop novel alternatives for proprietary use during the term of any resulting patents.

The selection of known materials to study was generally relatively simple since the prior art had shown that, in general, the simplest derivatives were the most effective from the dyeing point of view.

In 1986 Wella applied for a patent on the combination of 4-amino-3-methylphenol and 5-amino-2-methylphenol with either *p*-phenylenediamine or 2,5-diaminotoluene to produce "pure red shades". This combination was proposed as an alternative to the much used ternary combination using *p*-aminophenol. In spite of the fact that Schwartzkopf [12] had listed 3-methyl-4-aminophenol as an alternative to 4-aminophenol, the Wella application was granted in both the United States and Europe [21].

Wella [22] also obtained a patent on hair dye compositions, which they have commercialized, comprising 2-β-hydroxyethyl-*p*- phenylenediamine in combination with couplers selected from resorcinol, 2-methylresorcinol, 4-chlororesorcinol, 3,4-methylenedioxyphenol, 3-aminophenol and *N*-(2-hydroxyethyl)-3,4-methylenedioxyaniline, as being non-mutagenic. This primary intermediate was among a group of 2-hydroxyalkyl-*p*-phenylenediamines patented by Wella [23] with a priority date of 1978.

Prior to the grant of these "selection" or "combination" patents, oxidation dye patents had comprised compositions having dye precursors which were newly synthesized entities or were novel in that they had never been previously suggested as useful in oxidation dyeing. Patent applications for combinations of known dye precursors were generally rejected as being obvious or lacking in an inventive step.

The new paradigm holds a combination to be patentable if the applicant can show some purported difference in even one of the many facets of performance relative to the closest prior art combination. This has led to a spate of issued patents covering combinations of known ingredients and even of ingredients that had been previously used in commercial products but not in the specifically claimed combination.

In the author's opinion the concept of "general knowledge of one ordinarily skilled in the art" is no longer used in judging patentability with respect to "obviousness".

This is unfortunate, particularly in the light of the fact that cooperation among manufactures within the trade associations, notably in the European Union, in submitting toxicological data to obtain regulatory approval for hair dye ingredients has meant that it has long been common knowledge as to which ingredients were considered potentially useful in the event that the currently used materials failed to get approval. It is combinations incorporating these alternatives with commercially used materials in combinations, in which the alternative fulfills the same function as the material it replaces, that have been the main focus of these new patents.

As we look to the future, it is evident that these patents will create major problems for the industry if it should lose the approval for the use of *p*-phenylenediamine, *p*-aminophenol and 2,5-diaminotoluene.

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