188. *The Oxidation of Derivatives of* o-*Phenylenediamine. Part I. Isomeric Phenazine Pigments obtained by Oxidation of 2-Aminodiphenylamine Hydrochloride.*

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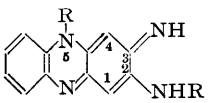
2-Aminodiphenylamine hydrochloride has been oxidised by *p*-benzoquinone. The crude oxidation product, after purification on alumina, yielded the known 2-anilino-3 : 5-dihydro-3-imino-5-phenylphenazine (anilino-*apo*safranine) accompanied by a similar pigment which is shown to be the isomer, 2-amino-3 : 5-dihydro-5-phenyl-3-phenyliminophenazine.

IT has been shown in these laboratories that ferric chloride oxidation of mono-substituted *N*-derivatives of *o*-phenylenediamine produces in good yields 2 : 5-substituted derivatives of 3 : 5-dihydro-3-iminophenazine. In this way anilino*apo*safranine (I; R = Ph) was obtained from 2-aminodiphenylamine hydrochloride.[1,2,3] These 2 : 5-substituted derivatives exhibit antituberculosis activity *in vitro* [1] and in mice,[4] and anilino*apo*safranine has been claimed to exert a curative effect in lepromatous leprosy.[5] It has now been shown that the crude ferric chloride oxidation product of 2-aminodiphenylamine hydrochloride contains, as well as anilino*apo*safranine (I; R = Ph), about 5—10% of an isomeric pigment for which the structure (II; R = Ph) is proposed.

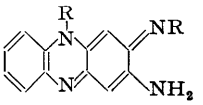
The early literature on the ferric chloride oxidation of 2-aminodiphenylamine has been surveyed by Barry and Belton.[2] According to Fischer and Dischinger [6] the main product of the reaction was (I; R = Ph). Kehrmann and Messinger,[7] however, maintained that the main oxidation product had the structure (II; R = Ph). Degradative experiments

[1] Barry, Belton, Conalty, and Twomey, *Nature*, 1948, **162**, 622.
[2] Barry and Belton, *Proc. Roy. Irish Acad.*, 1953, **55**, *B*, 149.
[3] Barry, Belton, Chambers, Conalty, Kelly, and Twomey, *ibid.*, p. 157.
[4] Barry, *Irish J. Med. Sci.*, 1951, 453.
[5] Allday and Barnes, *ibid.*, 1952, 421.
[6] Fischer and Dischinger, *Ber.*, 1896, **29**, 1602.
[7] Kehrmann and Messinger, *J. prakt. Chem.*, 1892, **46**, 568.

on the oxidation product carried out by Fischer and Heiler [8] which are discussed below finally convinced Kehrmann that (I; R = Ph) correctly represented the structure of anilino*apo*safranine. In the present paper it is shown that, when *p*-benzoquinone is used as oxidant in place of ferric chloride, 2-aminodiphenylamine hydrochloride yields as well as the *apo*safranine (I; R = Ph) an approximately equal amount of a second pigment which



(I)



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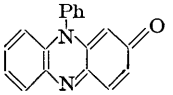


(III)

closely resembles it in properties. Evidence is presented which confirms the structure of anilino*apo*safranine and establishes that the second product is correctly represented by (II; R = Ph) and is identical with the product obtained in small amount by ferric chloride oxidation.

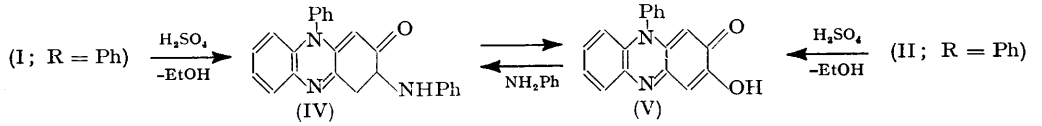
When an aqueous solution of *p*-benzoquinone is added with stirring to an aqueous solution of 2-aminodiphenylamine hydrochloride, a dark red powder separates, which consists for the most part of a mixture of the hydrochlorides of the two phenazines (I and II; R = Ph). The filtrate contains a number of other highly coloured materials only one of which (III) (*apo*safranone [9]) has so far been identified. The crude precipitate was recrystallised from alcohol, the hydrochloride of anilino*apo*safranine (I; R = Ph) for the most part remaining in solution; the crystalline hydrochloride of the isomer (II; R = Ph), which separated in an impure condition, was converted into the base which was purified by chromatography and then formed a dark red crystalline powder, m. p. 257—259°. The more soluble hydrochloride, recovered from the alcohol, was converted into the base and similarly purified, giving bright red crystals, m. p. 203—204°, identical with the anilino*apo*safranine (I; R = Ph) obtained in the ferric chloride oxidation.[2] The high-melting base (II; R = Ph) retains benzene tenaciously and was only obtained solvent-free after 10 hours' heating at 105° under reduced pressure. Like anilino*apo*safranine (I; R = Ph) it then gave analyses correct for $C_{24}H_{18}N_4$ and showed light-absorption maxima at 230, 272, and 455 mμ compared with 280 and 480 mμ for the former. The isomers may be readily distinguished by their different behaviour towards concentrated sulphuric acid and acetic anhydride. Anilino*apo*safranine (I; R = Ph) dissolves in sulphuric acid to a brown-red solution while the isomer forms a green-brown solution, and both solutions become fuchsin-red on dilution. On being warmed with acetic anhydride, the compound (I; R = Ph) forms a red-brown solution which blackens quickly, while the isomer gives a stable reddish-purple solution from which a crystalline monoacetyl derivative separates on cooling.

Molecular-weight determinations on the isomer (II; R = Ph) were not satisfactory, because of its relatively low solubility. The oxidative condensation was therefore effected with *N-cyclo*hexyl-*o*-phenylenediamine. In this case, whether ferric chloride or *p*-benzoquinone was used as oxidising agent, the only product identified appeared from its behaviour with sulphuric acid and acetic anhydride to have structure (II; R = *cyclo*hexyl). This compound was much more soluble than its phenyl analogue and molecular-weight determinations confirmed that we were dealing with a simple structure such as (II).

In agreement with Fischer and Heiler,[8] heating anilino*apo*safranine (I; R = Ph) in a sealed tube with alcoholic sulphuric acid gave a mixture of decomposition products from which anilino*apo*safranone (IV) and hydroxy*apo*safranone (V) were isolated. Similar treatment of the isomer (II; R = Ph) yielded, surprisingly, the same degradation products. It is clear that the anilino*apo*safranone (IV) could not result as a direct degradative product from a compound (II; R = Ph) but it could possibly be formed as a reversion product from the hydroxy*apo*safranone (V) and the liberated aniline; and this was shown to be correct by heating the hydroxy-ketone (V) with aniline and dilute sulphuric acid in alcohol in a sealed tube, anilino*apo*safranone (IV) being obtained in 50% yield. It was

[8] Fischer and Heiler, *Ber.*, 1893, **26**, 378.
[9] Kehrmann and Bürgin, *Ber.*, 1896, **29**, 1819.

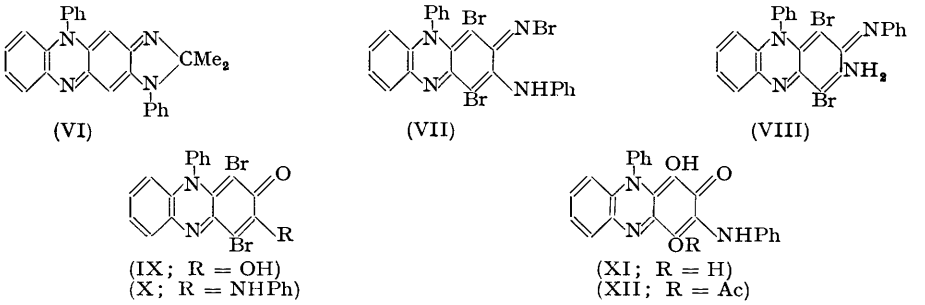
thus clear that these degradations did not provide certain evidence by which the structure (I; R = Ph) for anilino*apo*safranine could be established, and could as readily be adduced in favour of structure (II; R = Ph). Further examination of the isomeric pigments was therefore desirable.



Anilino*apo*safranine reacts readily in warm alcohol with 1-fluoro-2 : 4-dinitrobenzene to form highly insoluble glistening black needles, while with its isomer no reaction takes place under reflux except in the presence of anhydrous sodium acetate. The presence of an aromatic amino-group in the high-melting product is suggested by its behaviour on diazotisation and on treatment with nitrosobenzene. With sodium nitrite and dilute hydrochloric acid under the usual conditions, followed by boiling with alcohol, it gave an insoluble blue powder which has not been identified. A similar product was obtained on treatment in hypophosphorous acid solution with sodium nitrite and subsequent boiling. Again, the high-melting isomer with nitrosobenzene in alcohol slowly yielded a dark green crystalline powder which has not so far been identified. In contrast to this behaviour, anilino*apo*safranine was recovered for the most part unchanged from the diazotisation and the treatment with nitrosobenzene. Although not completely satisfactory these reactions are in agreement with the presence of an NH_2-group in the high-melting isomer.

Furthermore, if the *p*-benzoquinone oxidation of 2-aminodiphenylamine hydrochloride is effected in aqueous acetone, an orange-yellow crystalline base (VI) can be isolated, which shows a striking green-yellow fluorescence in solution. This is confirmed by the isolation of the same product (VI) when anilino*apo*safranine is warmed with acetone in acid solution. Similar glyoxalinophenazines have been made by using other ketones, and show a yellowish-green fluorescence in solution; they will be discussed in a later paper. In contrast with this behaviour of anilino*apo*safranine, treatment of the high-melting isomer with acetone in acid solution leads to products of low solubility in organic solvents and the solutions are not fluorescent. Here again the evidence supports formula (I; R = Ph) for anilino*apo*safranine and formula (II; R = Ph) for the high-melting isomer.

Again, the isomers (I and II; R = Ph) react in carbon tetrachloride solution with bromine or *N*-bromosuccinimide to give tribromo- and dibromo-derivatives, respectively. These are represented by (VII) and (VIII), two bromine atoms presumably entering the *ortho*-positions to the quinonoid system and in (VII) the third bromine atom replaces the imino-hydrogen. If these formulations are correct, then sealed-tube degradations of both bromo-compounds might be expected to give the identical dibromo-hydroxy*apo*safranone (IX) or anilino-dibromo*apo*safranone (X), a bromine atom being lost only from



(VII). [In one case, the anilino-compound (X) would be a reversion product formed as indicated above.] Unexpectedly all the bromine was eliminated from both the bromo-compounds, which each gave the anilinodihydroxy*apo*safranone (XI). This was converted into a monoacetyl derivative, which probably has the structure (XII) as it might be expected that hydrogen bonding would prevent the acylation of the hydroxyl group *ortho*

to the carbonyl group. The formation of the substance (XI) is readily understandable on the basis of the structures (I and II; R = Ph) for the isomeric phenazine pigments.

It should be emphasised that if 2-aminodiphenylamine base is oxidised by *p*-benzoquinone, a mixture of coloured products is obtained which is quite different from that got from the hydrochloride.

Experimental

Oxidation of 2-Aminodiphenylamine Hydrochloride.—(a) *With ferric chloride.* The amine hydrochloride (7·0 g.) in water (350 c.c.) was stirred for 1 hr. with aqueous ferric chloride (16·0 g. in 160 c.c.). The precipitate was dried (6·5 g.) and converted into the base with alcoholic sodium hydroxide. One-half of the dry product in benzene was chromatographed on alumina (Merck). Elution with benzene gave (i) a few crystals which showed a pink fluorescence in benzene, (ii) dark red crystals (0·3 g.; m. p. 257—259°), and (iii) bright red crystals (1·8 g.; m. p. 203—204°). A number of highly coloured bands remained on the column but were not further investigated. Fraction (ii), 2-*amino*-3 : 5-*dihydro*-5-*phenyl*-3-*phenyliminophenazine* (II; R = Ph), was recrystallised from benzene without change in m. p. (Found: C, 80·8; H, 5·2; N, 13·9. $C_{24}H_{18}N_4,\frac{1}{2}C_6H_6$ requires C, 81·0; H, 5·2; N, 14·0%). After drying at 105°/10 mm. for 10 hr., there was no change in m. p. (Found: C, 79·6; H, 5·1; N, 15·0. $C_{24}H_{18}N_4$ requires C, 79·6; H, 5·0; N, 15·5%). The compound is insoluble in water, slightly soluble in ether, sparingly soluble in alcohol. Fraction (iii) was recrystallised from benzene (Found: C, 79·1; H, 4·9; N, 15·3%) and was 2-anilino-3 : 5-dihydro-3-imino-5-phenylphenazine (I; R = Ph).

(b) *With* p-*benzoquinone.* The amine hydrochloride (11·0 g.) in hot water (300 c.c.) was stirred at 60° with *p*-benzoquinone (8·0 g.) in water (250 c.c.). The mixture was kept for 2 hr. and the precipitate dried (8·9 g.). Recrystallisation from alcohol gave a hydrochloride (4·4 g.) which was converted into the base and purified chromatographically. The m. p. and mixed m. p. proved its identity with the product (II; R = Ph) above. The alcoholic mother-liquor gave with sodium hydroxide a second base (4·0 g.), which was purified chromatographically. The main product in this fraction was anilino*apo*safranine (I; R = Ph).

Isolation of 2 : 10-*dihydro*-2-*oxo*-10-*phenylphenazine* (apo*safranone*). The filtrate from the previous preparation, after the separation of the above crude hydrochloride [prepn. (*b*)], when made alkaline with sodium hydroxide, gave a dark finely divided precipitate which was separated by centrifuging. The yield of crude material was very small and a number of filtrates from different preparations were combined. The dried product dissolved to the extent of 25% in benzene, leaving a black powder which was discarded. The benzene extract was chromatographed and gave as main product brown needles of *apo*safranone, m. p. 248—249° (yield <1%), identical with a sample prepared by the method of Kehrmann and Bürgin [9] (after chromatographic purification).

Derivatives of 2-*Amino*-3 : 5-*dihydro*-5-*phenyl*-3-*phenyliminophenazine.*—(i) The base was refluxed in alcohol with 1-fluoro-2 : 4-dinitrobenzene in the presence of anhydrous sodium acetate for 4 hr. The dark precipitate was washed with water and recrystallised from dioxan; the 2 : 4-*dinitrophenyl derivative* then formed dark green crystals, m. p. 270—272° after drying (3½ hr. at 105° under reduced pressure) (Found: C, 65·4; H, 4·1; N, 15·2. $C_{30}H_{20}O_4N_6,H_2O$ requires C, 65·9; H, 4·0; N, 15·4%). (ii) The base was refluxed for 10 min. with excess of acetic anhydride and cooled. The precipitated *acetyl derivative* was washed with light petroleum and recrystallised from benzene; it was a brown powder, m. p. 310° (decomp.) (Found: C, 77·4; H, 5·3; N, 13·9. $C_{26}H_{20}ON_4$ requires C, 77·2; H, 4·95; N, 13·9%). (iii) The base in benzene was refluxed for ½ hr. with excess of methyl sulphate. The deposited *methosulphate* recrystallised from alcohol as grass-green needles, m. p. 302—304° (decomp.) (Found: C, 63·3; H, 4·9; N, 11·6; S, 6·7. $C_{26}H_{24}O_4N_4S$ requires C, 63·9; H, 4·9; N, 11·5; S, 6·6%). (iv) Addition of concentrated hydrochloric acid to an alcoholic solution of the base gave the *salt* as green shimmering needles, m. p. >350° (Found: C, 69·6; H, 5·5; N, 13·3; Cl, 8·5. $C_{24}H_{18}N_4,HCl,H_2O$ requires C, 69·1; H, 5·0; N, 13·4; Cl, 8·5%).

2-*Amino*-5-cyclo*hexyl*-3-cyclo*hexylimino*-3 : 5-*dihydrophenazine.*—(a) *Ferric chloride oxidation.* *N-cyclo*Hexyl-*o*-phenylenediamine hydrochloride (7·7 g.) in alcohol (40 c.c.) and water (200 c.c.) was stirred with ferric chloride solution (34·0 g. in 180 c.c.). The precipitate (6·0 g.) was converted into the base, and recrystallised from benzene as an orange-red powder, m. p. 216—218° (Found: C, 77·4; H, 8·3; N, 14·4. $C_{24}H_{30}N_4,\frac{1}{4}C_6H_6$ requires C, 77·8; H, 8·0; N, 14·2%). This *phenazine* has also been obtained with m. p. 224—226°. No other product was isolated from this oxidation.

(b) p-*Benzoquinone oxidation.* The amine hydrochloride (7·5 g.) in 20% aqueous alcohol

(230 c.c.) was stirred for 2 hr. with a warm solution of *p*-benzoquinone (6·0 g. in 240 c.c. of water). The precipitate was converted into the base by alcoholic sodium hydroxide and recrystallised from benzene. It (4·6 g.) was proved by its m. p. and mixed m. p. to be identical with the compound got by the ferric chloride oxidation [*M* (cryoscopically in benzene), 385. $C_{24}H_{30}N_4$ requires *M*, 374].

Sealed-tube Degradations.—(a) *Anilino*apo*safranine*. The base (5·0 g.) with 10% sulphuric acid (10 c.c.) and alcohol (10 c.c.) was heated in a sealed tube at 180° for 4 hr. The mixture was then boiled with 10% aqueous sodium hydroxide. A benzene extract of the residue was chromatographed on alumina (Merck). The main band yielded dark-red glistening needles, m. p. 258—260° (decomp.) (about 50 mg.), which were dried at 105°/10 mm. for 10 hr. [Found: C, 78·9; H, 4·8; N, 11·3. Calc. for $C_{24}H_{17}ON_3$ (anilino*apo*safranone): C, 79·3; H, 4·7; N, 11·5%]. The alkaline filtrate was acidified with acetic acid, giving an orange-yellow flocculent precipitate which recrystallised from alcohol as orange-red needles, m. p. 280° (decomp.) (20 mg.) [Found: C, 74·1; H, 4·3; N, 9·6. Calc. for $C_{18}H_{12}O_2N_2$ (hydroxy*apo*safranone): C, 75·0; H, 4·2; N, 9·7%]. The methyl ether, prepared according to Fischer and Hepp's method,[11] agreed with their description of hydroxy*apo*safranone methyl ether.

(b) 2-*Amino*-3: 5-*dihydro*-5-*phenyl*-3-*phenyliminophenazine*. The degradation, carried out as above, gave anilino- and hydroxy-*apo*safranone in approximately the same yields.

*Condensation of Aniline with Hydroxy*apo*safranone*.—Hydroxy*apo*safranone (150 mg.), synthesised by Kehrmann's method,[10] was heated with alcohol (10 c.c.), aniline (1 c.c.), and 10% sulphuric acid (5 c.c.) at 180—200° for 3½ hr. Anilino*apo*safranone (75 mg.) was isolated.

Diazotisation of 2-*Amino*-3: 5-*dihydro*-5-*phenyl*-3-*phenyliminophenazine*.—(a) *With hypophosphorous acid*. The base (1 g.) in hypophosphorous acid (32%; 70 c.c.) was cooled to 0° and sodium nitrite (0·3 g.) added, the temperature being kept below 5°. The mixture was stirred for 4 hr. and allowed to reach room temperature. The solid product was refluxed with alcoholic ammonia, leaving undissolved a blue powder (0·6 g.) which did not melt and was insoluble in all organic solvents.

(b) *With hydrochloric acid*. This diazotisation was carried out in alcoholic solution by the standard method. Again the main product was a blue powder apparently identical with that got as in (*a*). It was recovered unchanged by addition of water to its solution in concentrated sulphuric acid (Found: C, 68·8; H, 3·6; N, 14·2%).

Attempted diazotisation of anilino*apo*safranine by these methods gave unchanged material.

Bromination of the Isomeric Pigments.—(a) *Of anilino*apo*safranine*. The base (2·8 g.) in carbon tetrachloride (300 c.c.) was stirred with bromine (2 c.c.) in the same solvent (50 c.c.). The precipitated hydrobromide was converted into the 1: 4: N^3-*tribromo-base* with alcoholic sodium hydroxide and recrystallised from benzene–light petroleum. It was a red powder, m. p. >360° (Found, after being heated for 4 hr. at 105°/10 mm.: Br, 35·9. $C_{24}H_{15}N_4Br_3,C_6H_6$ requires Br, 35·5%). Identical material was obtained when anilino*apo*safranine was heated under reflux in chloroform with *N*-bromosuccinimide.

(b) *Of* 2-*amino*-3: 5-*dihydro*-5-*phenyl*-3-*phenyliminophenazine*. The base (0·5 g.) was treated in chloroform (100 c.c.) with bromine (0·5 c.c.) in chloroform. The precipitate was treated with alcoholic sodium hydroxide and the recovered 1: 4-*dibromo-base* recrystallised from benzene as dark red needles, m. p. 242—244° (Found: Br, 28·8. $C_{24}H_{16}N_4Br_2,\frac{1}{2}C_6H_6$ requires Br, 28·6%). The same material was got when *N*-bromosuccinimide was heated in chloroform with the base.

Sealed-tube Degradation of the Bromo-derivatives.—Parallel experiments were conducted with the two bromo-derivatives. The hydrobromide of the bromo-compound (5 g.) was heated (4 hr.) in a sealed-tube with alcohol (10 c.c.) and 10% sulphuric acid (10 c.c.) at 180°. The mixture was then boiled with 10% aqueous sodium hydroxide (200 c.c.). The filtrate gave on acidification with acetic acid a reddish-yellow precipitate which was purified by repeated dissolution in alkali and reprecipitation with acetic acid. After recrystallisation from alcohol it was got as brown-red crystals (50 mg.) (Found: C, 73·5; H, 4·2; Br, 0. $C_{24}H_{17}O_3N_3$ requires C, 72·9; H, 4·3%). A few mg. of this 2-*anilino*-3: 5-*dihydro*-1: 4-*dihydroxy*-3-*oxo*-5-*phenylphenazine* were heated with acetic anhydride and a little pyridine. The product, recovered by dilution with water and recrystallised from methanol, formed brown-red needles, m. p. 230° (Found: Ac, 10·5. $C_{24}H_{16}O_3N_3{\cdot}CO{\cdot}CH_3$ requires Ac, 9·8%). Further treatment failed to raise the acetyl content above this figure.

5: 2′-*Dihydro*-2′: 2′-*dimethyl*-5: 1′-*diphenylglyoxalino*(5′: 4′-2: 3)*phenazine* (VI).—(a) *Oxidation*

[10] Kehrmann, *Ber.*, 1895, **28**, 1709.
[11] Fischer and Hepp, *Ber.*, 1896, **29**, 365.

of 2-aminodiphenylamine hydrochloride in aqueous acetone. The amine hydrochloride (4 g.) in 50% aqueous acetone (60 c.c.) was treated with hot aqueous *p*-benzoquinone (4 g. in 150 c.c.). The solution was made alkaline with sodium hydroxide, and the precipitate dried (3·8 g.) and extracted with boiling benzene, leaving a residue (0·8 g.). The extract was chromatographed on alumina (Merck). The main product, the *glyoxalinophenazine*, which was the first one eluted, showed a yellow-green fluorescence. It was obtained as orange yellow needles (2 g.), m. p. 236—237° (Found : C, 81·3; H, 6·2; N, 12·7. $C_{27}H_{22}N_4,\frac{1}{2}C_6H_6$ requires C, 81·8; H, 5·7; N, 12·7%) and retained benzene after 12 hours' heating at 105°/10 mm. The same material is obtained when ferric chloride is used in place of *p*-benzoquinone.

(b) *Condensation of acetone and anilino*apo*safranine.* The base (1 g.) in acetone (50 c.c.) containing syrupy phosphoric acid (10 c.c.) was heated on the water-bath for 15 min. The mixture was made alkaline and the separated solid dried and extracted with boiling benzene. On chromatography the same fluorescing material (m. p. and mixed m. p.) was obtained (0·2 g.).

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