Some Novel Halogenated Phenazine Derivatives

Dermot Twomey

Laboratories of the Medical Research Council of Ireland, Trinity College,
Dublin 2, Ireland

Received September 26, 1985

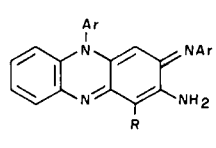
3-Amino-10-aryl-2-arylimino-2,10-dihydrophenazines **1** undergo iodination in the 4-position of the phenazine nucleus yielding compounds which are identical with those obtained by oxidation of appropriate *N*-aryl-*o*-phenylenediamines with sodium iodate in the presence of acid. Bromination also takes place in this position but a second bromine atom enters the *para*-position of the arylimino moiety. The isomeric 10-aryl-3-arylamino-2,10-dihydro-2-iminophenazines **2** yield unstable iodo-derivatives but undergo bromination in the 1-and 4-position of the phenazine nucleus and in the *ortho*- and *para*-positions of the arylamino substituent. Preliminary chlorination experiments indicate that the substitution pattern is analogous to that established for the brominated products. The removal of bromine and iodine from the phenazine ring by reaction with a primary or secondary amine and their replacement by hydrogen rather than by the amine residue is also recorded.

J. Heterocyclic Chem., **23**, 615 (1986).

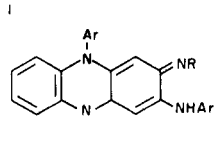
The oxidation of *N*-aryl-*o*-phenylenediamine derivatives has been the subject of a continuing investigation [1-4] in these laboratories for many years and has led to the development of a number of highly active antibacterial agents [5] one of which is now an established drug in the treatment of leprosy under the name clofazimine. When ferric chloride or *p*-benzoquinone was used as oxidant the principal reaction products were isomeric aposafranine derivatives having structures **1** and **2**. Other oxidising agents *e.g.* hydrogen peroxide, potassium dichromate, potasium permanganate, potassium ferricyanide or toluquinone also yielded these products in variable amounts, admixed with a variety of other products which have not been examined. However when *N*-phenyl-*o*-phenylenediamine was treated with sodium iodate in the presence of acid [6] a high yield of an iodine-containing material was obtained which after treatment with base had the composition $C_{24}H_{17}IN_4$. An identical product was obtained by treatment of the preformed phenazine **3** [3] with iodine in chloroform. Similarly *N*-(*p*-chlorophenyl)-*o*-phenylenediamine on reaction with sodium iodate yielded an iodo-derivative which was also obtained by treatment of the phenazine **4** with iodine. The same iodo-compounds were obtained in lower yield and in less pure form by treatment of the aryl-*o*-phenylenediamines with iodic or periodic acid. It is of interest that in a series of oxidation experiments on the phenylenediamines with iodate the phenazines **3** and **4** were frequently formed as minor by-products but the corresponding isomers *i.e.* **5** and **6** have not been detected - this may be of significance in determining the mechanism by which the oxidation reaction takes place.

Unlike **3** and **4** the iodo-products derived from them do not form *N*-acyl derivatives on reaction with acetic anhydride and conversely, preformed acyl derivatives of **3** and **4** do not yield iodo-derivatives on treatment with molecular iodine. These results seemed initially to indicate involvement of the amino group in the iodination process but a subsequent comparison of the ^1H nmr spectrum of **3** with that of the iodo compound derived from it showed that a singlet at δ 6.5 assigned to the proton in the 4-position of the phenazine nucleus was absent in the spectrum of the latter, which consequently must be represented by structure **7**. Similarly the iodo-compound derived from **4** had structure **8**. The failure to acylate **7** and **8** must therefore be attributed in part to steric factors. It is of interest that in the chlorination of 2-amino-1,4-benzoquinones with *t*-butyl hypochlorite Moore and Cajipe also found [9] that halogenation took place exclusively in the position *ortho* to the amino group. Furthermore these iodinated phenazines whether obtained by the oxidation procedure or by reaction of preformed phenazines with iodine also consisted exclusively of mono-substituted products. This was

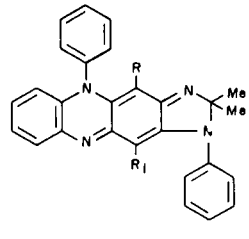
Diagram 1



1, R = H
3, R = H, Ar = C_6H_5
4, R = H, Ar = $C_6H_4Cl(4-)$
7, R = I, Ar = C_6H_5
8, R = I, Ar = $C_6H_4Cl(4-)$



2, R = H
5, R = H, Ar = C_6H_5
6, R = H, Ar = $C_6H_4Cl(4-)$



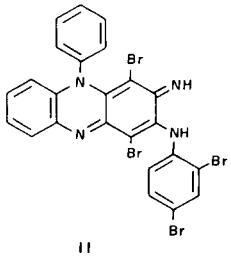
9, R = R_1 = H
10, R = H, R_1 = I

further exemplified by the quantitative conversion of the imidazophenazine **9** [3] into the mono iodo-derivative **10**, despite the close similarity of both quinoneimine positions.

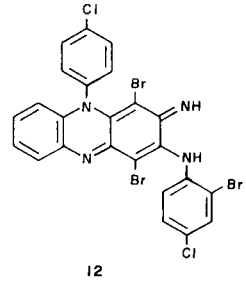
This facile introduction of an iodine atom into the phenazine nucleus prompted us to re-examine previously described bromination studies [10] where it was claimed that no bromine had entered the phenazine ring. As a result of further chemical investigation coupled with ^{1}H nmr examination it has now been established that one bromine atom consistently enters the 4-position of the phenazine nucleus and that in compounds where spatial conditions are favourable substitution of a second bromine atom in the 1-position also takes place. These brominated products, which were generally prepared by treatment of dilute chloroform solutions of the parent phenazines with excess bromine, separated as perbromides from which the base was liberated by treatment with alkali.

Bromination of anilinoaposafranine **5** [3] yielded a product which after removal of the alkali labile bromine was found to contain four bromine atoms. An examination of the ^{1}H nmr spectra of this material and the parent aposafranine showed that two of the bromine atoms had entered the 1- and 4-positions of the phenazine ring and that the other two had entered the *ortho*- and *para*-positions of the anilino residue to yield **11**. The correctness of these bromine assignments was further emphasized by the formation of a tribromo-derivative **12** in the bromination of **6** [11].

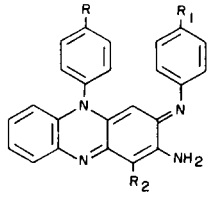
Diagram 2



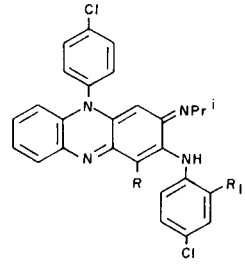
11



12



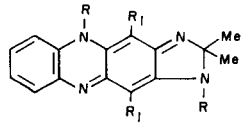
13, R = H, R_1 = R_2 = Br
14, R = R_1 = Cl, R_2 = Br



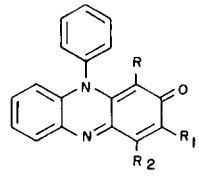
15, R = R_1 = H
16, R = R_1 = Br

In both of these compounds which undergo disubstitution of the phenazine nucleus there is an unsubstituted imine group. However any substituent on this nitrogen atom prevents the entry of a second bromine atom due presumably to spatial restrictions. Thus bromination of **3** yielded a dibromo derivative **13** in which one bromine atom has entered the 4-position of the phenazine ring and the second one has substituted in the *para*-position of the phenylimino grouping. Similarly bromination of **4** yielded a monobromo derivative **14** while bromination of **15** (clofazimine) [12] yielded a dibromo derivative **16**. On the other hand if the imino-nitrogen is incorporated into another heterocyclic system bromination resulted in di-substitution in the phenazine moiety. Thus treatment of the imidazophenazine **17** with bromine led to the formation of a perbromide containing five bromine atoms, three of which were removed by treatment with base. The resultant dibromo compound was shown by ^{1}H nmr to have structure **18**. A similar dibromo compound **20** was obtained from the dicyclohexyl analog **19** [13].

Diagram 3



17, R = C_6H_5, R_1 = H
18, R = C_6H_5, R_1 = Br
19, R = C_6H_{11}, R_1 = H
20, R = C_6H_{11}, R_1 = Br



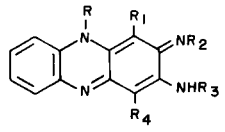
21, R = R_1 = R_2 = H
22, R = Br, R_1 = R_2 = H
23, R = R_2 = H, R_1 = NHC_6H_5
24, R = R_2 = Br, R_1 = $NHC_6H_3Br_2(2,4-)$
25, R = R_2 = H, R_1 = $NHC_6H_3Br_2(2,4-)$
26, R = R_2 = Br, R_1 = $NHC_6H_4Br(4-)$
27, R = Br, R_2 = H, R_1 = NHC_6H_{11}
28, R = Br R_2 = H, R_1 = pyrrolidin-1-yl
29, R = Br, R_2 = H, R_1 = NHC_6H_5
30, R = Br, R_2 = H, R_1 = $NHC_6H_3Br_2(2,4-)$

The influence of substituents in the 2- and 3-positions of the phenazine nucleus in determining the extent and direction of bromination was further shown by the reactions of a number of aposafranone derivatives with bromine. Bromination of aposafranone **21** yielded a monobromo-derivative which was shown to have structure **22** while bromination of anilinosposafranone **23** [3] yielded the expected tetrabromo-derivative **24** which was also obtained by bromination of 2,4-dibromoanilino-aposafranone **25**. Furthermore the concentrations at which these brominations are performed are critical - in some instances bromination of concentrated solutions (greater than one per cent) led to mixtures of partially brominated products which frequently proved difficult to resolve. In one experiment bromination of a 2.4 per cent chloroform solution of anilinoaposafranone yielded exclusively the highly interesting tribrominated product **26**.

In all these bromination experiments we have not identified any brominated compounds other than those in which substitution had taken place in the phenazine nucleus and/or in the aryl substituents in the 2- or 3-positions. It is of interest that in an investigation of related heterocycles *e.g.* 10-phenylphenothiazine and 10-phenylphenoxazine Jovanovic and Biehl have found [14] that treatment with bromine in acetic acid resulted in nuclear substitution only whereas treatment with pyridinium bromide perbromide led to substitution in the *para*-position of the 10-phenyl ring.

These brominated and iodinated phenazines on being heated in strong organic bases *e.g* primary or secondary amines underwent a number of interesting displacement reactions. Heating the iodo-compounds **7** and **8** in cyclohexylamine or pyrrolidine resulted in complete de-iodination and regeneration of the parent phenazines while heating **7** in refluxing aniline also resulted in removal of the iodine atom and formation of **35** [15]. In the case of the bromophenazines it has also been found possible to displace one or both halogen atoms from the phenazine nucleus. Generally the bromine atom in the 4-position is more labile than that in the 1-position and may be selectively removed under appropriate reaction conditions. Under more vigorous conditions *e.g.* longer heating periods or higher temperatures both halogen atoms are removed. Thus the bromoaposafranone **22** on heating with cyclohexylamine, pyrrolidine and aniline at 100° was quantitatively converted into **27**, **28** and **29** respectively, the bromine atom being totally inert under these conditions and the substitution of the nucleophile residues in the 3-position of the aposafranone system being in accord with literature precedent [16,17]. However heating the tetrabromoanilinoaposafranone **24** under the same conditions resulted in the removal of the bromine atom in the 4-position and the formation of **30**. Similarly when the tetrabromoanilinoaposafranine **11** was heated in cyclohexylamine at 100° the major product was the tribromo-derivative **31** while heating in refluxing cyclohexylamine for periods of 2-3 hours resulted in the removal of both nuclear bromine atoms and the formation of **32**, the removal of the bromine atom in position 1 resulting in a more favourable spatial arrangement which permitted reaction of the amine with the imine group [12]. A parallel result was obtained with the bromo compound **12**. Heating in cyclohexylamine at 100° resulted in the formation of **33** while heating in refluxing cyclohexylamine led to the formation of **34** in which removal of both nuclear bromine atoms was again accompanied by substitution of the cyclohexyl residue on the imine nitrogen atom. Treatment of the bromo compound **16** with cyclohexylamine at 100° resulted in displacement of the nuclear bromine atom and total transamination resulting again in the formation of **34**.

Diagram 4



31, R = C_6H_5, R_1 = Br, R_2 = R_4 = H, R_3 = $C_6H_3Br_2(2,4-)$
32, R = C_6H_5, R_1 = R_4 = H, R_2 = C_6H_{11}, R_3 = $C_6H_3Br_2(2,4-)$
33, R = $C_6H_4Cl(4-)$, R_1 = Br, R_2 = R_4 = H, R_3 = $C_6H_3Br(2-)Cl(4-)$
34, R = $C_6H_4Cl(4-)$, R_1 = R_4 = H, R_2 = C_6H_{11}, R_3 = $C_6H_3Br(2-)Cl(4-)$
35, R_1 = R_4 = H, R = R_2 = R_3 = C_6H_5
36, R = R_3 = C_6H_5, R_2 = H, R_1 = R_4 = Br
37, R = R_3 = C_6H_5, R_2 = R_4 = H, R_1 = Br
38, R = C_6H_5, R_1 = R_4 = Cl, R_2 = H, R_3 = $C_6H_3Cl_2(2,4-)$
39, R = $C_6H_4Cl(4-)$, R_1 = R_4 = Cl, R_2 = H, R_3 = $C_6H_3Cl_2(2,4-)$
40, R = $C_6H_4Cl(4-)$, R_1 = H, R_4 = Cl, R_2 = Pr^i, R_3 = $C_6H_3Cl_2(2,4-)$

The chlorination of these phenazines has not been fully examined but exploratory experiments employing sulfuryl chloride indicate that the products have the same substitution pattern as that established for the brominated compounds. Thus reaction of **5** with sulfuryl chloride in chloroform solution yielded a product which, after treatment with base, was found to be a tetrachloro compound having structure **38**. Compounds **6** and **15** when similarly treated yielded **39** and **40** respectively.

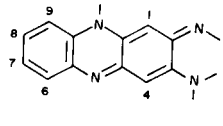
Table

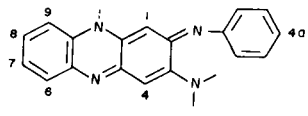
Analytical Data of other Halogenated Phenazines

Compound	mp [a]	Formula	C	H	Br	N
			Calcd. (Found)			
14	288-292 (A)	$C_{24}H_{15}BrCl_2N_4$	56.5 (55.8	2.9 2.8	15.7 15.2	11.0 10.7)
20	195-198 (B)	$C_{27}H_{34}Br_2N_4$	56.4 (56.5	5.9 5.6	27.9 28.3	9.8 9.6)
27	191-192 (A)	$C_{24}H_{22}BrN_3O$	64.8 (64.3	5.0 4.9	17.9 17.9	9.4 9.4)
28	180 dec. (A)	$C_{22}H_{18}BrN_3O$	62.9 (62.4	4.3 4.2	19.0 18.7	10.0 9.9)
29	225-230 (A)	$C_{24}H_{16}BrN_3O$	65.2 (65.1	3.6 3.4	18.1 18.1	9.5 9.4)
39	224-226 (A)	$C_{24}H_{13}Cl_5N_4$ [b]	54.2 (53.9	2.4 2.4	— —	10.4 10.5)
40	>280 (C)	$C_{27}H_{20}Cl_4N_4$ [c]	59.8 (59.0	3.7 3.2	— —	10.3 9.9)

[a] Recrystallization solvents: A = chloroform-ethanol, B = benzene-ethanol, C = chloroform-light petroleum (60-80°). [b] Calcd. Cl, 33.2. Found 32.9. [c] Calcd. Cl, 26.2. Found 26.6.

EXPERIMENTAL





3-Amino-2,10-dihydro-4-iodo-10-phenyl-2-phenyliminophenazine (**7**).

(a) A solution of sodium iodate monohydrate (7.6 g, 0.035 mole) in water (250 ml) was added dropwise with stirring to an aqueous ethanolic solution (50% v/v, 130 ml) of *N*-phenyl-*o*-phenylenediamine hydrochloride (3.6 g, 0.016 mole). After 6 hours at ambient temperature the reddish brown salt was collected, washed with water and basified (ethanolic sodium hydroxide). The base after chromatography on alumina was obtained as dark red needles (2.0 g, 50%) mp 218-220° (benzene). In concentrated sulfuric acid it had a pronounced bright red color which changed to pink on dilution; ^{1}H nmr (DMSO-d_6): δ 5.25 (s, 1H, H-1), 6.0 (s, 2H, NH_2), 6.6-6.4 (m, 1H, H-9), 7.1-6.6 (m, 12H, H-7, H-8 and other aromatics), 7.3-7.5 (m, 1H, H-6).

Anal. Calcd. for $C_{24}H_{17}IN_4$: C, 59.0; H, 3.5; I, 26.0; N, 11.5. Found: C, 58.8; H, 3.5; I, 25.7; N, 11.3.

(b) A chloroform solution of iodine was added to a chloroform solution of **3**. The mixture was stored overnight and the salt precipitated by dilution with benzene. The base after purification was identical, mp, tlc and color reactions with that described above.

Reaction of **7** with (a) Pyrrolidine.

A solution of **7** (0.61 g), in pyrrolidine (50 ml) was heated under reflux for 8 hours. The amine was removed and the residual solid purified by recrystallisation (benzene-ligroin). It was identified as **3** by mp, mixed mp, tlc and color reaction in concentrated sulfuric acid. The yield was 0.25 g, (55%).

Reaction of **7** with (b) Cyclohexylamine.

A solution of **7** (1.0 g) in cyclohexylamine (20 ml) was heated on a boiling water bath for 6 hours. Removal of the amine and purification of the residue as above yielded **3** (0.47 g, 63%)

Reaction of **7** with (c) Aniline.

A solution of the hydrochloride of **7** (0.9 g) in aniline (20 ml) was refluxed for 15 minutes. The cooled solution was poured into diethyl ether and the precipitated salt collected. It was converted to the base which after chromatography (alumina) and recrystallisation (benzene-ligroin) had mp 235-237° undepressed on admixture with an authentic sample of **35**. It also had a characteristic blue color in concentrated sulfuric acid solution. The yield was 0.4 g (53%).

3-Amino-10-(4-chlorophenyl)-2-(4-chlorophenylimino)-2,10-dihydro-4-iodophenazine (**8**).

This compound was obtained by treatment of a 50% aqueous ethanolic solution of *N*-(*p*-chlorophenyl)-*o*-phenylenediamine hydrochloride with an aqueous solution of sodium iodate and by treatment of a chloroform solution of **4** with a chloroform solution of iodine. The base after chromatography on alumina had mp 257-260° dec (benzene).

Anal. Calcd. for $C_{24}H_{15}Cl_2IN_4$: C, 51.7; H, 2.6; Cl, 12.7; I, 22.8; N, 10.1. Found: C, 52.1; H, 2.8; Cl, 13.1; I, 22.4; N, 10.0.

This compound on heating in refluxing cyclohexylamine was converted to the iodine free material, 3-amino-10-(4-chlorophenyl)-2-(4-chlorophenylimino)-2,10-dihydrophenazine (**4**) mp 275-277°, recorded mp 255-257° [3].

Anal. Calcd. for $C_{24}H_{16}Cl_2N_4$: C, 66.8; H, 3.7; Cl, 16.5; N, 13.0. Found: C, 66.9; H, 3.7; Cl, 16.5; N, 12.8.

5′,2′-Dihydro-2′,2-dimethyl-5,1′-diphenyl-11-iodoimidazo[5′,4′-2,3]phenazine (**10**).

A benzene solution of the imidazo derivative **9** (0.5 g, 0.0012 mole) was added to a benzene solution of iodine (0.8 g, 0.003 mole). On keeping overnight a grass green precipitate formed. This was collected, washed with a little benzene and neutralised (ethanolic ammonia). The base (0.56 g, 86%) was chromatographed and recrystallized twice from methanol. It was obtained as orange yellow needles, mp 230-231° dec; ^{1}H nmr (DMSO-d_6): δ 7.85-6.85 (m, 13H, H-6-H-9 and other aromatics), 6.5-6.25 (m, 1H, H-9), 5.32 (s, 1H, H-1), 1.48 (s, 6H, 2 × Me).

Anal. Calcd. for $C_{27}H_{21}IN_4$: C, 61.4; H, 4.0; I, 24.1; N, 10.6. Found: C, 61.5; H, 3.9; I. 23.7; N, 10.5.

1,4-Dibromo-3-(2,4-dibromoanilino)-2,10-dihydro-2-imino-10-phenylphenazine (**11**).

A solution of **5** (2.0 g, 0.0055 mole) in chloroform (350 ml) was treated with a carbon tetrachloride solution of bromine (6.4 g, 0.04 mole). The solution was stored at ambient temperature for 72 hours when a dark green highly crystalline solid separated slowly. This was collected and treated with ethanolic sodium hydroxide. The base which was purified chromatographically on alumina was obtained as dark red needles (1.3 g, 35%), mp 225-230° dec (chloroform-ethanol). It had a characteristic inky blue color in concentrated sulfuric acid which changed to a bright red on dilution; ^{1}H nmr: singlets at δ 6.93 and 5.14 assigned to protons in the quinoneimine ring of the unbrominated product are absent. A doublet at 6.83 (*ortho*-coupling) and a doublet at 7.72 (*meta*-coupling) establish a 1,2,4-trisubstitution pattern in the aromatic ring.

Anal. Calcd. for $C_{24}H_{14}Br_4N_4$: C, 42.5; H, 2.1; Br, 47.2; N, 8.3. Found: C, 42.1; H, 2.1; Br, 47.2; N, 8.1.

3-(2-Bromo-4-chloroanilino)-10-(4-chlorophenyl)-1,4-dibromo-2,10-dihydro-2-iminophenazine (**12**).

A solution of **6** (4.3 g, 0.01 mole) in chloroform (300 ml) was mixed with a carbon tetrachloride solution of bromine (9.6 g, 0.06 mole). The salt separated slowly and was collected after 8 hours. The base (3.48 g, 52%), after chromatographic purification on alumina, had mp 206-210° dec (chloroform-methanol); ^{1}H nmr (DMSO-d_6): δ 9.45 (s, 1H, NH), 8.25 (s, 1H, NH), 7.95-7.80 (m, 1H, H-6), 7.65-7.45 (m, 3H, aromatic), 7.4-7.1 (m, 5H, aromatic), 6.88 (d, 1H, aromatic), 6.85-6.65 (m, 1H, H-9).

Anal. Calcd. for $C_{24}H_{13}Br_3Cl_2N_4$: C, 43.1; H, 1.9; Br, 35.9; Cl, 10.6; N, 8.4. Found: C, 43.0; H, 1.8; Br, 35.7; Cl, 10.6; N, 8.2.

3-Amino-4-bromo-2-(4-bromophenylimino)-2,10-dihydro-10-phenylphenazine (**13**).

A solution of **3** (0.5 g) in chloroform (80 ml) was mixed with a carbon tetrachloride solution of bromine (1.6 g). After 6 hours the precipitated salt was collected and converted to the base which was chromatographed (alumina). It had mp 244-245° (ethanol); ^{1}H nmr (DMSO-d_6): a singlet at 5.23 assigned to H-1 is common to the spectra of the unbrominated and brominated products. A singlet at δ 6.55 assigned to H-4 is not seen in the spectrum of the latter. A doublet showing strong *ortho*-coupling is seen at δ 6.8-6.4 indicating a *para*-disubstituted phenyl group *i.e.* the second bromine atom has replaced H-4a.

Anal. Calcd. for $C_{24}H_{16}Br_2N_4$: C, 55.4; H, 3.0; Br, 30.8; N, 10.8. Found: C, 55.2; H, 2.8; Br, 30.5; N, 10.6

4-Bromo-3-(2-bromo-4-chloroanilino)-10-(4-chlorophenyl)-2,10-dihydro-2-isopropyliminophenazine (**16**).

A solution of bromine (6.4 g, 0.04 mole) in carbon tetrachloride was added dropwise with stirring to a solution of **15** (5.0 g, 0.01 mole) in chloroform (300 ml). The mixture was kept for 8 hours and the precipitated salt then collected and basified. The base after chromatography on alumina was obtained as dark red needles (5.2 g, 78%) mp 193-195° (ethanol); ^{1}H nmr (deuteriochloroform): a peak at δ 5.25 assigned to H-1 is visible but the expected peak at 6.8 (H-4) is absent so that a bromine atom has substituted in this position. A doublet at 6.88 (*ortho*-coupling) and a doublet at 7.55 (meta-coupling) establish the presence of a 1,2,4-trisubstituted aromatic ring. This is the ring in the 2-position of the phenazine nucleus since the protons in the other aromatic ring *ortho* to the nitrogen atom were identified as a doublet at δ 7.70.

Anal. Calcd. for $C_{27}H_{20}Br_2Cl_2N_4$: C, 51.3; H, 3.2; Br, 25.4; Cl, 11.3; N, 8.9. Found: C, 51.4; H, 3.2; Br, 25.4; Cl, 11.2; N, 8.9.

4,11-Dibromo-5′,2′-dihydro-2′,2′-dimethyl-5,1′-diphenylimidazo[5′,4′-2,3]-phenazine (**18**).

Treatment of a chloroform solution of **17** with a chloroform solution of bromine resulted in quantitative formation of a pentabromo derivative

mp 220° dec (ethanol).

Anal. Calcd. for $C_{27}H_{20}Br_5N_4$: C, 40.5; H, 2.5; Br, 50.0; N, 7.0. Found: C, 40.4; H, 2.7; Br, 50.2; N, 6.8.

This material on treatment with base is smoothly converted to **18** which after chromatography (alumina) was obtained as orange yellow needles mp 247-250° dec (acetone); ^{1}H nmr: singlets at δ 5.75 and 5.36 assigned to protons H-1 and H-4 in the spectrum of **17** are not seen in the spectrum of **18**.

Anal. Calcd. for $C_{27}H_{20}Br_2N_4$: C, 57.9; H, 3.6; Br, 28.6; N, 10.0. Found: C, 57.6; H, 3.3; Br, 28.6; N, 10.0.

1-Bromo-2,10-dihydro-2-oxo-10-phenylphenazine (**22**).

A solution of aposafranone (**21**) (5.09 g, 0.018 mole) in chloroform (400 ml) was treated with a carbon tetrachloride solution of bromine (12.8 g, 0.08 mole) and the mixture stored overnight in refrigerator. The precipitated reddish brown salt was collected and basified (ethanolic ammonia). The base (5.8 g, 88%) had mp 228-230° dec (ethanol); ^{1}H nmr: a doublet at δ 5.53 assigned to H-1 in the spectrum of aposafranone is not seen in the spectrum of **22**.

Anal. Calcd. for $C_{18}H_{11}BrN_2O$: C, 61.5; H, 3.1; Br, 22.8; N, 8.0. Found: C, 61.6; H, 3.0; Br, 21.9; N, 7.8.

1,4-Dibromo-3-(2,4-dibromanilino)-2,10-dihydro-2-oxo-10-phenylphenazine (**24**).

A solution of **23** (3.0 g, 0.0082 mole) in chloroform (650 ml) was treated dropwise with a chloroform solution of bromine (12.8 g, 0.08 mole). The mixture was stirred for one hour and stored in refrigerator overnight. The precipitated solid was collected and treated with ethanolic sodium hydroxide. The base (3.6 g, 64%) had mp 219-221° (chloroform-ethanol); ^{1}H nmr (deuteriochloroform): the quinoneimine protons are not seen in the spectrum which also reveals the presence of a 1,2,4-trisubstituted aromatic ring.

Anal. Calcd. for $C_{24}H_{13}Br_4N_3O$: C, 42.4; H, 1.9; Br, 47.1; N, 6.2. Found: C, 42.2; H, 1.8; Br, 47.5; N, 6.2.

The presence of a 1,2,4-trisubstituted aromatic ring was further confirmed by bromination of **25** when **24** was also obtained.

3-(2,4-Dibromoanilino)-2,10-dihydro-2-oxo-10-phenylphenazine (**25**).

A mixture of hydroxyaposafranone (8.6 g, 0.03 mole) and 2,4-dibromoaniline (10.0 g, 0.04 mole) in nitrobenzene (35 ml) was heated at 180° for three and a half hours. The solvent was removed by steam distillation and the residual solid shaken with methanol (30 ml) and then extracted with boiling benzene. The benzene extract was chromatographed (alumina) and the product (2.6 g, 24%) further purified by recrystallizatoin from ethanol. It had mp 255-258°.

Anal. Calcd. for $C_{24}H_{15}Br_2N_3O$: C, 55.3; H, 2.9; Br, 30.7; N, 8.1. Found: C, 55.3; H, 2.8; Br, 30.4; N, 8.1.

3-(4-Bromoanilino)-1,4-dibromo-2,10-dihydro-2-oxo-10-phenylphenazine (**26**).

A solution of bromine (16.0 g, 0.1 mole) in carbon tetrachloride (25 ml) was added dropwise with stirring to a solution of **24** (6.0 g, 0.016 mole) in chloroform (250 ml). The precipitate which formed immediately was collected after 1 hour, washed with ether and basified. The analytical sample was obtained as dark red needles mp 225-226° (chloroform); ^{1}H nmr (deuteriochloroform): signals assigned to the quinoneimine protons are not seen, a doublet with *ortho*-coupling at δ 6.97 suggests a *para*-disubstituted aromatic ring.

Anal. Calcd. for $C_{24}H_{14}Br_3N_3O$: C, 48.0; H, 2.3; Br, 40.0; N, 7.0. Found: C, 47.9; H, 2.4; Br, 40.1; N, 6.9.

1-Bromo-3-(2,4-dibromoanilino)-2,10-dihydro-2-oxo-10-phenylphenazine (**30**).

The tetrabromo-derivative **24** (1.0 g) was dissolved in cyclohexylamine (20 ml) and the solution refluxed for 2 hours. The amine was removed and the residue purified by recrystallisation (twice) from chloroform-methanol). It had mp 228-230°; ^{1}H nmr (deuteriochloroform): a singlet at δ 7.26 indicates that the bromine in the 4-position of the phenazine nucleus has been replaced by hydrogen.

Anal. Calcd. for $C_{24}H_{14}Br_3N_3O.H_2O$: C, 46.6; H, 2.6; Br, 38.8; N, 6.8. Found: C, 46.7; H, 2.1; Br, 38.6; N, 6.9.

1-Bromo-3-(2,4-dibromoanilino)-2,10-dihydro-2-imino-10-phenylphenazine (**31**).

The tetrabromo compound **11** (1.0 g) was heated in refluxing cyclohexylamine (25.0 ml) for 30 minutes. The amine was removed by steam distillation and the residual solid chromatographed (alumina) and recrystallised (chloroform-ethanol). It decomposed slowly at 205-215°; ^{1}H nmr (deuteriochloroform): singlet at δ 6.90 indicates that the bromine atom in the 4-position has been replaced by a proton.

Anal. Calcd. For $C_{24}H_{15}Br_3N_4$: C, 48.1; H, 2.5; Br, 40.1; N, 9.4. Found: C, 47.9; H, 2.4; Br, 39.7; N, 9.3.

2-Cyclohexylimino-3-(2,4-dibromoanilino)-2,10-dihydro-10-phenylphenazine (**32**).

The tetrabromo compound **11** (2.0 g) was heated in refluxing cyclohexylamine (60 ml) for 2 hours. The amine was removed, the residual solid extracted with benzene (2 × 40 ml) and the combined benzene extracts chromatographed (alumina). The product was obtained as reddish brown needles (0.5 g) mp 240-242° (chloroform-ethanol); ^{1}H nmr (deuteriochloroform): singlets at δ 5.18 and 6.79 indicate that protons H-1 and H-4 are present.

Anal. Calcd. for $C_{30}H_{26}Br_2N_4$: C, 59.8; H, 4.3; Br, 26.6; N, 9.3. Found: C, 59.7; H, 4.7; Br, 25.7; N, 9.3.

1-Bromo-3-(2-bromo-4-chloranilino)-10-(4-chlorophenyl)-2,10-dihydro-2-iminophenazine (**33**).

A solution of **12** (0.5 g) in cyclohexylamine (15 ml) was heated under reflux for 60 minutes. The amine was removed and the residual solid extracted with benzene (3 × 20 ml). The combined benzene extracts were chromatographed and the product (0.31 g, 70%) further purified by recrystallisation. It had mp 220° (chloroform-ethanol). A singlet at δ 6.85 absent in the spectrum of 12 is consistent with the presence of proton H-4 indicating replacement of bromine by hydrogen.

Anal. Calcd. for $C_{24}H_{14}Br_2Cl_2N_4$: C, 48.9; H, 2.4; Br, 27.2; N, 9.4. Found: C, 49.2; H, 2.4; Br, 26.8; N, 9.4.

3-(2-Bromo-4-chloranilino)-10-(4-chlorophenyl)-2-cyclohexylimino-2,10-dihydrophenazine (**34**).

A solution of **12** in cyclohexylamine was refluxed for one and a half hours and the product recovered and purified as described above. It had mp 234-235°; ^{1}H nmr (deuteriochloroform): δ 6.82 (s, 1H, H-4), 5.26 (s, 1H, H-1), 3.15 (m, 1H, cyclohexyl bridgehead proton), 2.00-1.00 (m, 10H, cyclohexyl).

Anal. Calcd. for $C_{30}H_{25}BrCl_2N_4$: C, 60.8; H, 4.2; Br, 13.5; Cl, 12.0; N, 9.5. Found: C, 60.9; H, 4.0; Br, 13.6; Cl, 12.0; N, 9.6.

3-Anilino-1,4-dibromo-2,10-dihydro-2-imino-10-phenylphenazine (**36**).

The pentabromo compound (4.9 g) obtained from **17** was catalytically hydrogenated (Pt/C, 5%) in ethanolic suspension in a Parr low pressure hydrogenator for 6 hours. The catalyst was removed and the pale green filtrate diluted with water and stored in refrigerator overnight. The off-white precipitate was collected, dried and redissolved in a mixture of benzene-ethanol. Addition of an ethanolic solution of *p*-benzoquinone caused an immediate darkening in color and rapid formation of a highly crystalline dark red precipitate (2.29 g, 72%) which was chromatographically pure. The analytical sample had mp 195-196° (benzene-methanol); ^{1}H nmr (deuteriochloroform): the peaks assigned to the quinoneimine protons are absent.

Anal. Calcd. for $C_{24}H_{16}Br_2N_4$: C, 55.4; H, 3.0; Br, 30.8; N, 10.8. Found: C, 55.8; H, 3.1; Br, 30.3; N, 10.5.

3-Anilino-1-bromo-2,10-dihydro-2-imino-10-phenylphenazine (**37**).

A solution of **36** (3 g) in cyclohexylamine (45 ml) was refluxed for 1½ hours. The amine was removed and the residual sticky solid extracted with boiling benzene (3 × 40 ml). The combined benzene extracts were chromatographed (alumina), the solvent removed from the main dark red fraction and the residue (1.7 g, 67%) further purified by recrystallisation from chlorofom-methanol. It had mp 193-195°; ^{1}H nmr (deuteriochloroform): a peak at δ 6.9 indicates that the bromine atom in the 4-position of the phenazine nucleus has been replaced by a proton.

Anal. Calcd. for $C_{24}H_{17}BrN_4$: C, 65.3; H, 3.9; Br, 18.1; N, 12.7. Found: C, 65.3; H, 4.2; Br, 18.0; N, 12.2.

1,4-Dichloro-3-(2,4-dichloroanilino)-2,10-dihydro-2-imino-10-phenylphenazine (**38**).

A solution of **5** (2.7 g, 0.0074 mole) in chloroform was treated with a large excess of sulfuryl chloride (5 ml) and the mixture stored at ambient temperature for 72 hours. Removal of the solvent and basification of the residual solid yielded the product which after recrystallisation from chloroform-ethanol [2] was obtained as reddish brown needles (1.6 g, 43%) mp 290°; ^{1}H nmr (deuteriochloroform): singlets at δ 6.93 and 5.14 in the spectrum of **5** are absent indicating replacement of both quinonimine protons by chlorine. A doublet at δ 6.87 (*ortho*-coupling) and a double doublet at 7.17 is consistent with the presence of 1,2,4-trisubstituted aromatic ring.

Anal. Calcd. for $C_{24}H_{14}Cl_4N_4$: C, 57.6; H, 2.8; Cl, 28.4; N, 11.2. Found: C, 57.4; H, 2.8; Cl, 28.4; N, 11.2.

Acknowledgements.

I am indebted to my colleageus Drs. J. G. Belton and R. S. McElhinney for many helpful discussions. I am grateful to May & Baker Ltd. (Dagenham) for the provision of microanalytical data and particularly to Mr. M. B. Vine for the determination and interpretation of the ^{1}H nmr spectra. The expert technical assistance of Ms. Mary McNelis is also gratefully acknowledged.

REFERENCES AND NOTES

[1] V. C. Barry, J. G. Belton, M. L. Conalty and D. Twomey, *Nature*, (London), **162**, 622 (1948).

[2] V. C. Barry, J. G. Belton, J. F. Chambers, M. L. Conalty, R. Kelly and D. Twomey, *Proc. Roy. Irish Acad.*, **55B** 157 (1953).

[3] V. C. Barry, J. G. Belton, J. F. O'Sullivan and D. Twomey, *J. Chem. Soc.*, 888 (1956).

[4] V. C. Barry, J. G. Belton, J. M. Denneny, D. W. Edward, J. F. O'Sullivan, D. Twomey and F. Winder, *Nature* (London), **178**, 1013 (1957).

[5] V. C. Barry, M. L. Conalty and E. E. Gaffney, *J. Pharm. Pharmacol.*, **8**, 1089 (1956).

[6] No reaction takes place in the absence of acid although sodium iodate *per se* is an effective oxidant [7,8].

[7] J. M. Bruce and F. K. Sutcliffe, *J. Chem. Soc.*, 4820 (1956).

[8] J. G. Belton, C. N. O'Callaghan and D. Twomey, *Proc. Roy. Irish Acad.*, **62B**, 9 (1961).

[9] H. W. Moore and G. Cajipe, *Synthesis*, 49 (1973).

[10] V. C. Barry, J. G. Belton, J. F. O'Sullivan and D. Twomey, *J. Chem. Soc.*, 3217 (1959).

[11] V. C. Barry, J. G. Belton, J. F. O'Sullivan and D. Twomey, *J. Chem. Soc.*, 896 (1956).

[12] V. C. Barry, J. G. Belton, J. F. O'Sullivan and D. Twomey, *J. Chem. Soc.*, 859 (1958).

[13] V. C. Barry, J. G. Belton, J. F. O'Sullivan and D. Twomey, *J. Chem. Soc.*, 3347 (1956).

[14] V. Jovanovic and E. R. Biehl, *J. Org. Chem.*, **49**, 1905 (1984).

[15] V. C. Barry, J. G. Belton, J. F. O'Sullivan and D. Twomey, *J. Chem. Soc.*, 859 (1958).

[16] O. Fischer and E. Hepp, *Ber.*, **28**, 2283 (1895).

[17] O. Fischer and E. Hepp, *Ber.*, **38**, 3435 (1905).

[18] D. Twomey, unpublished results.

[19] Maximum yields have not been determined.

[20] In every instance the ^{1}H nmr spectra of the uniodinated and unbrominated materials were determined for reference purposes. With some compounds only the critical proton assignments are recorded.