348. *The Preparation of Benziminazoles and Benzoxazoles from Schiff's Bases. Part II.*

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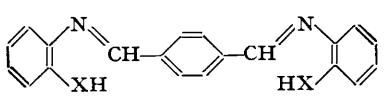
The method described in Part I has been extended, principally to the synthesis of *Bz*-substituted benzoxazoles. New reagents are described for this reaction, and a mechanism is postulated.

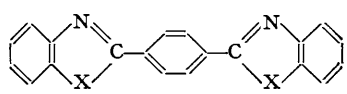
In Part I (*J.*, 1949, 2971) the preparation of 2-phenyl-benziminazoles and -benzoxazoles, by dehydrogenation of their corresponding Schiff's bases with lead tetra-acetate, was described. With one exception, the compounds described therein were without substituents in the *Bz*-ring. In order to examine the generality of the method and to prepare compounds of potential medicinal or chemotherapeutic interest (to be reported later, see however B.P. Appln. 8,680/49) the synthesis of *Bz*-substituted benziminazoles and benzoxazoles was attempted.

In a few cases, when aromatic aldehydes were condensed with substituted *o*-phenylenediamines, stable, highly coloured, recrystallisable compounds were formed. These were assumed to be Schiff's bases and were dehydrogenated by lead tetra-acetate in the normal manner. In other cases, the condensation products were converted into benziminazoles merely by being heated or on recrystallisation. Thus, *p*-nitrobenzaldehyde reacts with *N*-methyl-*o*-phenylenediamine (in 50% acetic acid) to give a bright red solid which on recrystallisation (from ethanol or pyridine) is converted into 2-*p*-nitrophenyl-1-methylbenziminazole. This compound is identical with that prepared by Wiedenhagen and Train (*Ber.*, 1942, **75**, 1936) by cupric acetate oxidation of the mixed aldehyde and amine. Again, 3 : 4-diaminobenzonitrile and *p*-cyanobenzaldehyde react in boiling glacial acetic acid to give a pale yellow solid (m. p. *ca.* 300°) which is unaffected by lead tetra-acetate. If the components react in ethanol, an orange-red solid is obtained which if heated slowly also melts at *ca.* 300°, but if heated rapidly melts at *ca.* 180°. On boiling the red solid with acetic acid or recrystallising it from benzonitrile, it becomes identical with the pale yellow one [5(6)-cyano-2-*p*-cyanophenylbenziminazole]. In this type of reaction Elderfeld *et al.* (*J. Amer. Chem. Soc.*, 1948, **70**, 44) have supplied spectroscopic evidence that the initial product is a benziminazoline and have suggested that this spontaneously oxidises to a benziminazole. [Cf. also the work on the condensation of aldehydes with *o*-amino-thiophenols by Lankelma and Sharnoff (*J. Amer. Chem. Soc.*, 1931, **53**, 2654).] In view of these results, little work was done on the preparation of *Bz*-substituted benziminazoles.

Condensation of aldehydes with substituted *o*-amino-phenols gave stable Schiff's bases (soluble in dilute alkali) in all the cases examined and ring-closure by heat or recrystallisation was never observed. From these Schiff's bases 2-phenylbenzoxazoles containing a variety of substituents in the *Bz*-ring, *e.g.*, chloro, bromo, nitro, dinitro, cyano, carbomethoxy, methyl, and sulphamyl, were prepared by the method described in Part I (*loc. cit.*). The Schiff's base (I; X = O), terephthalidenebis-*o*-aminophenol, was converted into *p*-phenylenebis-2-benzoxazole (II; X = O) and, in addition, two heterocyclic groups (pyridyl and furyl) and the trichloromethyl group (from chloral) were inserted in the 2-position of benzoxazole.



(I.)

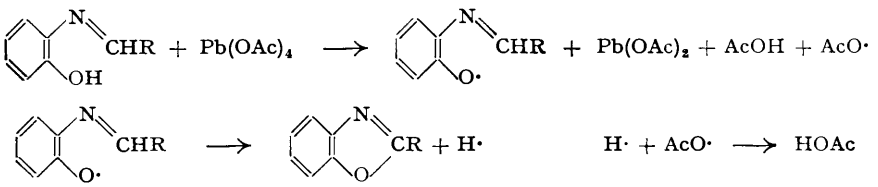


(II.)

Terephthalidenebis-*o*-phenylenediamine (I; X = NH) was prepared and, although oxidation proceeded normally, the product could not be purified. *p*-Phenylenebis-2-1-methylbenziminazole (II; X = NMe) was prepared.

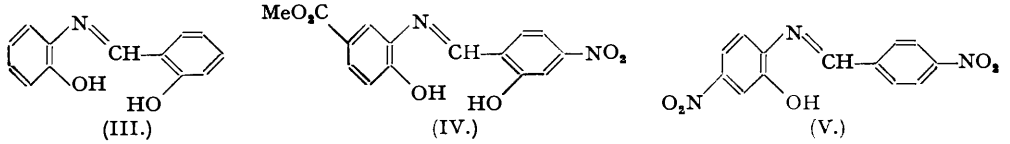
The preparation of 2-*p*-nitrophenylbenzoxazole from its Schiff's base was attempted by means of a number of other reagents. These included cupric acetate, persulphates, periodic acid, mercuric acetate, sodium bismuthate (cf. Rigby, *Nature*, 1949, **164**, 185), benzoquinone, chloranil, *N*-bromosuccinimide, and benzoyl peroxide. From the action of the first named, the Schiff's base was recovered quantitatively and unchanged. No benzoxazole was isolated from the reaction with persulphate or periodic acid. The other reagents all gave the desired product, chloranil, *N*-bromosuccinimide, and benzoyl peroxide being particularly active (see Experimental); the yields from mercuric acetate and sodium bismuthate were very small. Desai, Hunter, and Khalidi (*J.*, 1934, 1186) unsuccessfully attempted this ring-closure by means of hydrogen peroxide and potassium ferricyanide.

Considering the preparation of benzoxazoles (where stable Schiff's bases are precursors), it is probable that ring closure by lead tetra-acetate proceeds by a free-radical mechanism, the stages of which may be represented as follows :



Some evidence for these views is supplied by the following : (*a*) reagents found to cause easy ring closure are known to generate free radicals, (*b*) when 4-nitro-2-*p*-nitrobenzylideneaminotoluene reacted in boiling acetic acid with lead tetra-acetate the Schiff's base was quantitatively recovered, (*c*) the first step in the above scheme has been postulated by Cosgrove and Waters (*J.*, 1949, 3189) in the reaction of phenols with benzoyl peroxide, (*d*) the yields obtained in the *simple* cases (cf. Part I, *loc. cit.*) appear to be unrelated to the electronic character of the substituent in the 2-phenyl ring (cf. the recent work on the Pschorr reaction by Hey and Osbond, *J.*, 1949, 3172), (*e*) parallel work (in collaboration with D. G. Wibberley; to be reported later) has shown that the azo-methine linkage may be replaced by the ethylene bond (leading to coumarones). From these considerations it was deduced that sulphuryl chloride, reacting with the liberation of chlorine atoms, would effect ring closure. This was found to be the case (see Experimental).

If the idea of primary attack on the hydroxy-group is accepted, this will explain the low yield obtained in the preparation of 2-*o*-hydroxyphenylbenzoxazole where the Schiff's base (III) has two hydroxy-groups exposed, and attack on only one can lead to the desired cyclisation. In this respect, and again revealing the effects of substituents, a good yield was obtained in the



(III.) (IV.) (V.)

oxidation of (IV) whereas (V) was extremely resistant to attack by lead tetra-acetate. Finally, if the benzoxazoles contained halogen in the 6-position, they appeared to be prepared with especial ease.

The intermediates required in this work were mostly prepared by established methods. 3 : 4-Diaminobenzonitrile has been prepared by Bogert and Wise (*J. Amer. Chem. Soc.*, 1910, **32**, 1494) and by Borsche *et al.* (*Ber.*, 1916, **49**, 2233), but no yields are given. Catalytic reduction of 3-nitro-4-aminobenzonitrile was found satisfactory for this preparation, and the route described in the experimental section more convenient than those employed by the above workers.

Experimental.

(All m. p.s were determined with Anschütz thermometers.) (See also B.P. Applns. 2478/49 and 8680/49.)

p-Acetamidobenzaldoxime.—Hydroxylamine hydrochloride (10 g.), dissolved in a mixture of pyridine (45 ml.) and ethanol (50 ml.), was added to a solution of *p*-acetamidobenzaldehyde (20 g.) in pyridine (100 ml.) and ethanol (25 ml.). The mixture was refluxed for 40 minutes, the solvents removed by vacuum distillation on the steam-bath, and water (250 ml.) added to the residual oil to cause complete

precipitation of the product. Filtration and recrystallisation of this from water gave *p*-acetamidobenzaldoxime (19 g.; m. p. 210°) (Found: N, 15·7. Calc. for $C_9H_{10}O_2N_2$: N, 15·7%).

p-*Acetamidobenzonitrile.*—*p*-Acetamidobenzaldoxime (100 g.) was refluxed (30 minutes) with acetic anhydride (400 ml.), the mixture was cooled, diluted with water (3000 ml.) and neutralised with 50% sodium hydroxide solution. Filtration followed by recrystallisation (from water) gave *p*-acetamidobenzonitrile (87 g.; m. p. 206·5°) (Found: N, 17·3. Calc. for $C_9H_8ON_2$: N, 17·5%).

3-*Nitro*-4-*aminobenzonitrile.*—*p*-Acetamidobenzonitrile (50 g.) was added during 1 hour to a mixture of sulphuric acid (300 ml.; *d* 1·84) and potassium nitrate (67 g.) maintained below 0°. The mixture was kept at 0° for 2 hours, and then poured on ice, and the crude 3-nitro-4-acetamidobenzonitrile removed by filtration. Hydrolysis by refluxing sulphuric acid (30 ml.; *d* 1·84) and water (270 ml.) for 30 minutes, followed by two recrystallisations from water, gave 3-nitro-4-aminobenzonitrile (40 g.; m. p. 163°) (Found: N, 25·4. Calc. for $C_7H_5O_2N_3$: N, 25·7%).

3 : 4-*Diaminobenzonitrile.*—A suspension of 3-nitro-4-aminobenzonitrile (5 g.) in ethanol (120 ml.) was hydrogenated at room temperature in the presence of Adams's catalyst (initial hydrogen pressure: 50 lbs. per sq. in.). Reduction was complete within 15 minutes, after which the product was isolated by evaporation of the solvent. Recrystallisation from water gave 3 : 4-diaminobenzonitrile (3·5 g.; m. p. 146°) as white needles becoming pink in the air (Found: N, 31·7. Calc. for $C_7H_7N_3$: N, 31·6%). The quinoxaline, 6-*cyano*-2 : 3-*diphenylquinoxaline* (from benzil), formed white needles, m. p. 184° (Found: N, 13·8. $C_{21}H_{13}N_3$ requires N, 13·7%).

Schiff's Bases.—The Schiff's bases, detailed in Table I, were prepared by the general method described in Part I (*loc. cit.*), or by the use of 50% acetic acid in place of ethanol.

TABLE I.

Schiff's base.	Crystn. solvent.	Colour.	M. p.	Yield, %.	Analysis, N%, found.	required.
N-p′-*Nitrobenzylidene*-4-*methyl*-o-*phenylenediamine*	A	maroon	137°	64	16·7	16·5
N-p′-*Acetamidobenzylidene*-4-*methoxy*-o-*phenylenediamine*	A	greenish-yellow	174	70	15·1	14·8
Terephthalidenebis-o-*phenylenediamine*	F	orange	212—214	95	17·9	17·8
5-*Chloro*-2-(p-*cyanobenzylideneamino*)-*phenol*	C	yellow	202—204	82	[1]	[1]
4-*Nitro*-2-*benzylideneaminophenol* [2]	A	yellow	195	82	11·85	11·6
4-*Nitro*-2-(p-*nitrobenzylideneamino*)-*phenol*	A	yellow	239—240	88	14·8	14·6
4-*Nitro*-2-(p-*acetamidobenzylideneamino*)-*phenol*	E	yellow	249—250	98	13·8	14·0
5-*Nitro*-2-(p-*nitrobenzylideneamino*)-*phenol*	E	brown	261—263	90	14·7	14·6
5-*Nitro*-2-(p-*cyanobenzylideneamino*)-*phenol*	E	yellow	236—237	98	15·7	15·7
4 : 6-*Dinitro*-2-(p-*nitrobenzylideneamino*)-*phenol*	E	pale yellow	228—229	80	16·7	16·9
2-(p-*Nitrobenzylideneamino*)-4-*cyanophenol*	A	deep yellow	232—233	90	15·7	15·7
2-(p-*Cyanobenzylideneamino*)-4-*cyanophenol*	aq. C	biscuit	216	68	16·5	17·0
2-(p-*Nitrobenzylideneamino*)-4-*carbomethoxyphenol*	A	yellow	211—212	71	9·17	9·33
2-(p-*Nitrosalicylideneamino*)-4-*carbomethoxyphenol*	A	deep red	248—249	82	8·69	8·86
3-(p′-*Nitrobenzylideneamino*)-p-*cresol*	A	golden yellow	202—203	82	11·1	10·9
2-(p-*Nitrobenzylideneamino*)-4-*sulphonamidophenol*	E	bright yellow	256	90	[3]	[3]
2-(p-*Acetamidobenzylideneamino*)-4-*carbomethoxyphenol*	D	biscuit	232—233	65	9·08	8·97
2-(p-*Acetamidobenzylideneamino*)-4-*sulphonamidophenol*	aq. C	pale yellow	193	90	[4]	[4]
Terephthalidenebis-*o*-aminophenol	B	yellow	220—221 [5]	95	[6]	[6]

Crystallisation solvents used were: A = ethanol, B = *n*-butanol, C = glacial acetic acid, D = dioxan, E = benzonitrile, and F = pyridine.

[1] Found: N, 10·3; Cl, 13·5. $C_{14}H_9ON_2Cl$ requires N, 10·9; Cl, 13·8%. [2] Raiford and Linsk (*J. Amer. Chem. Soc.*, 1945, **67**, 878). [3] Found: N, 13·0; S, 9·87. $C_{13}H_{11}O_5N_3S$ requires N, 13·1; S, 9·97%. [4] Found: N, 12·5; S, 9·47. $C_{15}H_{15}O_4N_3S$ requires N, 12·6; S, 9·61%. [5] Levi (*Gazzetta*, 1929, **59**, 544) claims m. p. 213°. [6] Found: C, 76·8; H, 4·7; N, 9·06. Calc. for $C_{20}H_{16}O_2N_2$: C, 76·0; H, 5·06; N, 8·86%.

Benziminazoles and *Benzoxazoles.*—Unless otherwise stated, the benziminazoles and benzoxazoles, detailed in Table II, were obtained by the general method described in Part I (*loc. cit.*).

2-p-*Nitrophenylbenzoxazole by Means of Other Reagents.*—(*a*) *Chloranil.* 2-(*p*-Nitrobenzylideneamino)-phenol (1 g.) and chloranil (1 g.) were boiled under reflux in xylene (30 ml.) for 3 hours. The hot solution was filtered and, on cooling, 2-*p*-nitrophenylbenzoxazole (0·72 g.), m. p. 268°, was obtained.

(*b*) *Benzoyl peroxide.* The above Schiff's base (1 g.) and benzoyl peroxide (1 g.) were heated under

reflux in chloroform (50 ml.) for 90 minutes. Evaporation of the solvent followed by removal of benzoic acid (dilute alkali) gave a crude product which, after recrystallisation (from xylene), gave 2-*p*-nitrophenylbenzoxazole (0·5 g.), m. p. 268°.

TABLE II.

Compound.	Crystn. solvent.	Colour.	M. p.	Yield, %.	Analysis, N%, found.	required.
Benziminazoles.						
5(6)-*Cyano*-2-p-*nitrophenyl* [1]	PhCN	yellow	348°	56 *	20·9	21·2
5(6)-*Cyano*-2-p-*cyanophenyl* [1]	$PhNO_2$	pale yellow	346—347	41 *	23·3	22·9
2-p-*Nitrophenyl*-5(6)-*methyl*	aq. EtOH	orange	205	86	16·3	16·6
2-*p*-Nitrophenyl-1-methyl [1] [2]	EtOH	pale yellow	214	47 *	[3]	[3]
p-*Phenylenebis*-2-1-*methylbenziminazole* †	dioxan	white	288—289	25	16·4	16·6
Benzoxazoles.						
6-*Chloro*-2-p-*cyanophenyl*	AcOH	white	194—195	95	[4]	[4]
6-*Chloro*-2-p-*chlorophenyl*	EtOH	white	148—149	61 *	[5]	[5]
6-*Bromo*-2-p-*cyanophenyl* †	AcOH	pink	215	98	9·51	9·37
5-*Nitro*-2-*phenyl*	EtOH	cream	172	90	11·7	11·7
5-*Nitro*-2-p-*nitrophenyl*	PhCN	buff	257—258	70	14·6	14·7
5-*Nitro*-2-p-*acetamidophenyl*	dioxan	pale yellow	259—260	85	14·3	14·1
6-*Nitro*-2-p-*nitrophenyl* [6]	PhCN	pale yellow	221	10	14·4	14·7
6-*Nitro*-2-p-*cyanophenyl*	AcOH	yellow	205	60	15·6	15·8
5 : 7-*Dinitro*-2-p-*nitrophenyl*	nitromethane	pale yellow	208—209	80	17·1	17·0
5-*Cyano*-2-p-*nitrophenyl*	AcOH	yellow	296—298	55	15·7	15·8
5-*Cyano*-2-p-*cyanophenyl*	xylene	white	277—278	70	[7]	[7]
5-*Carbomethoxy*-2-p-*nitrophenyl*	AcOH	pink	198—199	80	9·24	9·40
5-*Carbomethoxy*-2-(2-*hydroxy*-4-*nitrophenyl*)	dioxan	yellow	242—243	85	[8]	[8]
5-*Carbomethoxy*-2-(p-*acetamidophenyl*) [9]	AcOH	salmon pink	274	95	9·06	9·03
5-*Carbomethoxy*-2-2′-*pyridyl*	*n*-BuOH	buff	168—169	80	10·9	11·0
5-*Methyl*-2-p-*nitrophenyl*	EtOH	pale yellow	209	90	11·2	11·0
5-*Sulphonamido*-2-p-*nitrophenyl*	AcOH	pale yellow	254—255	90	[10]	[10]
5-*Sulphonamido*-2-p-*acetamidophenyl* [11]	$PhNO_2$	pink	327—329	86	[12]	[12]
5-*Sulphonamido*-2-2′-*pyridyl*	water	brown	[13]	86	15·6	15·3
p-*Phenylenebis*-2′-*benzoxazole*	ethyl benzoate	yellow	354	84	[14]	[14]
2-*o*-Hydroxyphenyl	aq. AcOH	pale yellow	123—124	26	6·63	6·63
2-*Trichloromethyl* [15]	aq. EtOH	white [16]	57	60	[17]	[17]
2-Furyl	aq. EtOH	pale yellow	82—84	70	7·76	7·57

* Schiff's base not isolated; yield calculated on the amine.

† Schiff's base not purified.

[1] Dehydrogenation occurs on recrystallisation or on heating the precursor. [2] *Methochloride*, white plates (from water), m. p. 255° (Found: C, 58·6; H, 5·4; N, 13·1; Cl, 11·6. $C_{15}H_{14}O_2N_3Cl$ requires C, 59·3; H, 4·6; N, 13·8; Cl, 11·7%). [3] Found: C, 66·3; H, 4·18. Calc. for $C_{14}H_{11}O_2N_3$: C, 66·4; H, 4·35%. [4] Found: Cl, 13·5. $C_{14}H_7ON_2Cl$ requires Cl, 13·9%. [5] Found: Cl, 27·0. $C_{13}H_7ONCl_2$ requires Cl, 26·9%. [6] Oxidation carried out in boiling glacial acetic acid and an excess of lead tetra-acetate employed. [7] Found: C, 74·0; H, 2·8; N, 17·4. $C_{15}H_7ON_3$ requires C, 73·5; H, 2·9; N, 17·1%. [8] Found: C, 57·9; H, 3·3; N, 8·8. $C_{15}H_{10}O_6N_2$ requires C, 57·3; H, 3·2; N, 8·9%. [9] Hydrolysis with 50% sulphuric acid gives 2-p-*aminophenylbenzoxazole*-5-*carboxylic acid* (m. p. >300° decomp.) (Found: N, 11·0. $C_{14}H_{10}O_3N_2$ requires N, 11·0%). [10] Found: N, 13·1; S, 9·7. $C_{13}H_9O_5N_3S$ requires N, 13·2; S, 10·0%. [11] Acid hydrolysis, followed by neutralisation, gave 5-*sulphonamido*-2-p-*aminophenylbenzoxazole* (m. p. 290—291°) (Found: N, 14·0; S, 10·9. $C_{13}H_{11}O_3N_3S$ requires N, 14·5; S, 11·1%); *hydrochloride* (from dilute hydrochloric acid), colourless plates (m. p. 242° decomp.) Found: N, 12·2; Cl, 10·2. $C_{13}H_{11}O_3N_3S,HCl,H_2O$ requires N, 12·2; Cl, 10·3%). [12] Found: N, 12·4; S, 9·95. $C_{15}H_{13}O_4N_3S$ requires N, 12·7; S, 9·6%. [13] Depends upon rate of heating; *ca.* 230°. [14] Found: C, 77·1; H, 4·1; N, 9·3. $C_{20}H_{12}O_2N_2$ requires C, 76·9; H, 3·85; N, 8·9%. [15] Prepared from 2-(2 : 2 : 2-*trichloroethylideneamino*)*phenol* (m. p. 101°) (Found: N, 5·9. $C_8H_6ONCl_3$ requires N, 5·9%), which was obtained by interaction of chloral and *o*-aminophenol in glacial acetic acid. [16] White needles becoming purple in the air. [17] Found: Cl, 44·5. $C_8H_4ONCl_3$ requires Cl, 45·0%.

(*c*) N-*Bromosuccinimide*. The Schiff's base (1 g.) and *N*-bromosuccinimide (0·83 g.) were boiled under reflux in dry carbon tetrachloride for 3 minutes. The solvent was removed and the residue washed with hot water and recrystallised twice from xylene to give pale yellow needles (0·4 g.), m. p. 268°.

(*d*) *Sulphuryl chloride*. The Schiff's base (1 g.) in benzene (30 ml.) was treated with sulphuryl chloride (0·5 ml.), and the mixture boiled under reflux for 30 minutes. The product (m. p. 261°) separated on cooling and was recrystallised from xylene. Yield 0·4 g. (m. p. 268°).

Mixed m. p.s with material prepared by lead tetra-acetate oxidation (Part I, *loc. cit.*) were carried out in each of the above cases.

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