177. *The Synthesis and Reactions of Certain 6-Substituted Benzimidazo[1,2-c]quinazolines.*

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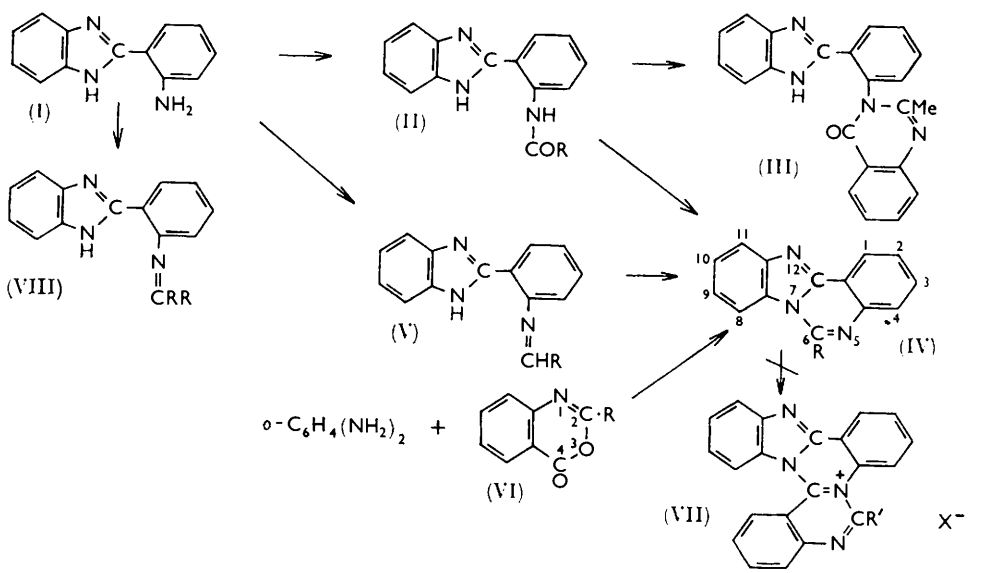
Various syntheses of certain 6-substituted benzimidazo[1,2-*c*]quinazolines, and particularly of the 6-*o*-aminophenyl member, have been critically investigated. The first method, based on the cyclisation of acyl derivatives of 2-*o*-aminophenylbenzimidazole, has been considerably improved. A second (and novel) method, based on the oxidation of the Schiff's bases formed from the aminophenylbenzimidazole and aryl aldehydes, provides a wide variety of the 6-arylbenzimidazoquinazolines, usually in high yield. A third synthesis has little value because of the low yield.

The reactions of 6-*o*-aminophenylbenzimidazoquinazoline have been studied in some detail. Further cyclisation of its acyl derivatives, to afford a second fused pyrimidine ring, did not succeed. The amine gives diazonium salts, which on treatment with sodium hydrogen carbonate and sodium hydroxide in turn, afford novel substituted benzimidazoles, the structure and several of the reactions of which have been elucidated. The amine very readily undergoes an acid-catalysed condensation with acetone to form an azomethine: the latter and its salts show considerable stability. 2-*o*-Aminophenylbenzimidazole forms similar stable azomethines.

The object of this investigation was the synthesis and study of various 6-substituted benzimidazo[1,2-*c*]quinazolines (IV). Our prime interest lay in the synthesis of the 6-*o*-aminophenyl member (IV; R = *o*-$C_6H_4{\cdot}NH_2$), and the investigation of its possible conversion into salts of type (VII), the reactions of its diazonium salts, and its methylation.

Three synthetic routes to benzimidazoquinazolines of type (IV) have been studied.



Preliminary experiments showed that 2-*o*-aminophenylbenzimidazole (I) did not condense with anthranilic or acetylanthranilic acid in the presence of phosphorus trichloride, phosphoryl chloride, or other reagents. Further, condensation with 2-methyl-3,1-benzoxazin-4-one (acetanthranil) (VI; R = Me) in an attempted synthesis of 2-[*o*-(*o*-acetamido)benzamidophenyl]benzimidazole (II; R = *o*-$C_6H_4{\cdot}NHAc$), gave only 6-methylbenzimidazo[1,2-*c*]quinazoline (IV; R = Me), indicating that the reagent (VI;

R = Me) had served solely to acetylate the amine (I) and that the product (II; R = Me) had then undergone normal cyclisation to the quinazoline (IV; R = Me).

In our first route, therefore, the benzimidazole (I) was converted in 90% yield by the action of *o*-nitrobenzoyl chloride in pyridine into the 2-*o*-nitrobenzamido-derivative (II; R = *o*-$C_6H_4{\cdot}NO_2$), which was reduced in 70% yield by zinc dust and acetic acid, also in pyridine, to the required 2-*o*-aminobenzamido-derivative (II; R = *o*-$C_6H_4{\cdot}NH_2$). When this compound was heated alone at 280° under reduced pressure, or with a phosphorus pentoxide–pyridine mixture, or with polyphosphoric acid, it underwent the required cyclisation to the benzimidazoquinazoline (IV; R = *o*-$C_6H_4{\cdot}NH_2$). The 2-*p*-nitrobenzamido-derivative (II; R = *p*-$C_6H_4{\cdot}NO_2$) was prepared similarly to the *o*-nitro-compound and then reduced to the 2-*p*-aminobenzamido-derivative (II; R = *p*-$C_6H_4{\cdot}NH_2$), which on heating underwent cyclisation to the quinazoline (IV; R = *p*-$C_6H_4{\cdot}NH_2$). The *o*-nitrobenzamido-compound was also readily converted into the benzimidazoquinazoline (IV; R = *o*-$C_6H_4{\cdot}NO_2$), which however, when reduced even under very mild conditions, gave the amino-derivative (IV; R = *o*-$C_6H_4{\cdot}NH_2$) in very low yield; the *p*-isomer (IV; R = *p*-$C_6H_4{\cdot}NO_2$) on attempted reduction gave a similar result. Nitrobenzamido-groups in compounds of type (II) should therefore be reduced to aminobenzamido-groups before cyclisation in order to obtain in good yield the corresponding aminoquinazolines of type (IV).

It is noteworthy that when the compound (II; R = *o*-$C_6H_4{\cdot}NH_2$) was acetylated and then heated, either alone at 300°/15 mm. or with phosphoryl chloride in toluene, the product was almost certainly the quinazolone (III), for it was not identical with the acetyl derivative of the authentic benzimidazoquinazoline (IV; R = *o*-$C_6H_4{\cdot}NH_2$), and its infrared spectrum showed a band at 3200 cm.$^{-1}$, attributed to the :NH group in the imidazole ring, and a strong :CO band at 1660 cm.$^{-1}$, but no absorption in the 1575—1515 cm.$^{-1}$ region which could be decisively attributed to the " amide-II " band of a ·CO·NH· group.

A second (and novel) synthesis has some analogy to Kilroe Smith and Stephen's preparation [1] of 2-arylquinazolines by the oxidation of various *o*-(benzylideneamino)-benzamides. 2-*o*-Aminophenylbenzimidazole (I) was condensed with *o*-nitrobenzaldehyde to give in 95% yield the azomethine (V; R = *o*-$C_6H_4{\cdot}NO_2$), which when oxidised with boiling acetone–permanganate rapidly gave the benzimidazoquinazoline (IV; R = *o*-$C_6H_4{\cdot}NO_2$) in 84% yield. This synthetic route proves of wide application with many aryl aldehydes (cf. Tables 1 and 2). Even *o*-aminobenzaldehyde gives in 80% yield the azomethine (V; R = *o*-$C_6H_4{\cdot}NH_2$), which can be directly oxidised to the quinazoline (IV; R = *o*-$C_6H_4{\cdot}NH_2$) in 70% yield: this route is of value since the amino-compound (IV; R = *o*-$C_6H_4{\cdot}NH_2$) cannot be profitably obtained by the reduction of the nitro-analogue (IV; R = *o*-$C_6H_4{\cdot}NO_2$). Aryl aldehydes containing phenolic groups give the lowest yields of those which we have studied, probably owing to destructive oxidation by the permanganate.

It is noteworthy that the *p*-hydroxybenzylidene member (V; R = *p*-$C_6H_4{\cdot}OH$) decomposes at its melting point to form phenol and the parent benzimidazo[1,2-*c*]-quinazoline (IV; R = H), a novel type of thermal decomposition.

The mechanism of the oxidative cyclisation of the azomethines (V) to the benzimidazo-quinazolines (IV) is unknown: it is possible that the azomethine (V) is converted first into an isomeric 6,7-dihydro-derivative of the quinazoline (IV), which then undergoes the familiar aromatisation by dehydrogenation.

The third method was based on Ghosh's condensation [2] of *o*-phenylenediamine with 2-benzamidomethyl-3,1-benzoxazin-4-one (VI; R = $CH_2{\cdot}NH{\cdot}CO{\cdot}Ph$) to form 6-benz-amidomethylbenzimidazo[1,2-*c*]quinazoline (IV; R = $CH_2{\cdot}NH{\cdot}CO{\cdot}Ph$). The use of 2-*o*-nitrophenyl-3,1-benzoxazin-4-one (VI; R = *o*-$C_6H_4{\cdot}NO_2$) in this reaction gave the

[1] Kilroe, Smith and Stephen, *Tetrahedron*, 1957, **1**, 38.
[2] Ghosh, *J. Indian Chem. Soc.*, 1937, **14**, 411.

required benzimidazoquinazoline (IV; R = *o*-C_6H_4·NO_2) in only low yield, the chief product being the benzimidazole (II; R = *o*-C_6H_4·NO_2). In view of this result, and the laborious preparation of suitably substituted derivatives of the compound (VI), this method was not further investigated. Our low yield of the quinazoline is in harmony with Zentmyer and Wagner's observation [3] that 2-(*o*-substituted phenyl)-3,1-benzoxazin-4-ones do not readily react with primary amines to form the corresponding quinazolones.

The two heterocyclic rings in the benzimidazoquinazoline structure (IV) contain in effect a diamidine system having a common central nitrogen atom, and the stability of this system might render difficult the formation of further fused rings. We have however investigated in some detail the possible cyclisation of the compound (IV; R = *o*-C_6H_4·NHAc) by means of acids to salts of structure (VII; R′ = Me), but without success. To attain greater reactivity in the side-chain, we have attempted to prepare the thio-derivative (IV; R = *o*-C_6H_4·NH·CSMe); this compound could not be satisfactorily purified and gave no evidence of the required cyclisation. Attempts to prepare the thioformyl compound (IV; R = *o*-C_6H_4·NH·CSH) by the use of dithioformyl derivatives also failed. Furthermore, the attempted conversion of the compound (III) into the chloride (VII; R′ = Me, X = Cl) by the action of phosphorus oxychloride, with or without the pentachloride, gave the hydrochloride of the amino-compound (I). The synthesis of the ring system (VII) was therefore abandoned.

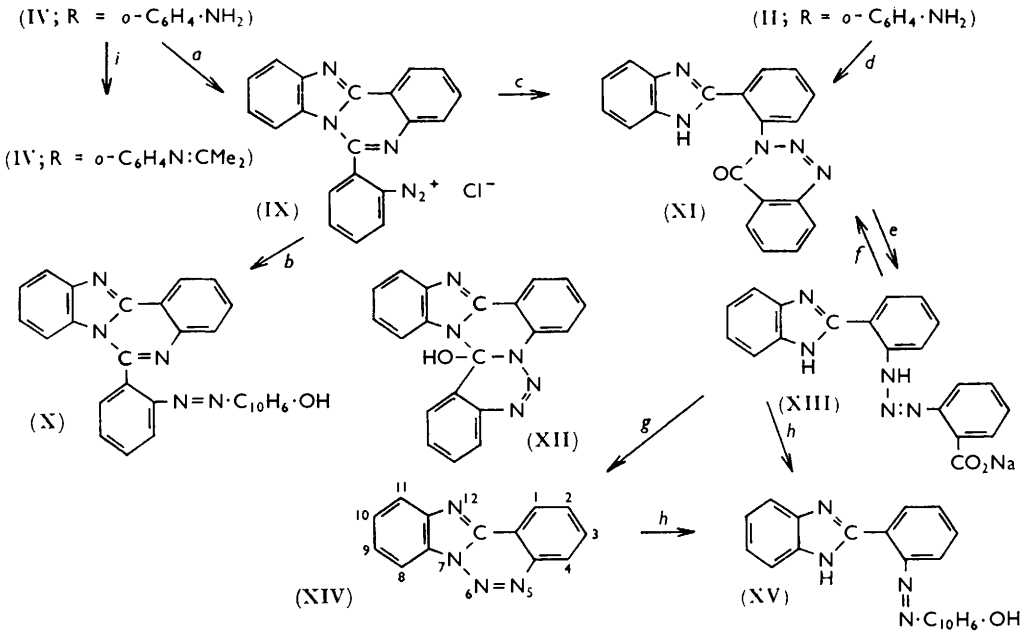
2-*o*-Aminophenylbenzimidazole (I) and 6-*o*-aminophenylbenzimidazo[1,2-*c*]quinazoline (IV; R = *o*-C_6H_4·NH_2) have one property in common, namely, that of forming stable basic alkylideneamino-compounds by acid-catalysed condensation with suitable ketones. A hot ethanolic solution of the amine (I), when treated with acetone containing hydriodic acid, furnished the yellowish-green hydriodide of 2-*o*-isopropylideneaminophenylbenzimidazole (VIII; R = R′ = Me), which with alkali gave the colourless base. The amine (I), with ethyl methyl ketone in ethanolic hydrogen chloride, similarly gave the yellow hydrochloride of the 2-*o*-s-butylideneaminophenyl derivative (VIII; R = Me, R′ = Et) whose hydriodide and hydrochloride show in solution an intense yellow-green and green fluorescence, respectively.

The benzimidazoquinazoline (IV; R = *o*-C_6H_4·NH_2) condenses with acetone containing hydriodic acid, to give the very pale yellow hydriodide of the 6-*o*-isopropylideneaminophenyl derivative (IV; R = *o*-C_6H_4·N:CMe_2); this salt is formed even when a solution of the quinazoline (IV; R = *o*-C_6H_4·NH_2) in acetone containing methyl iodide is boiled under reflux. The corresponding base is cream-coloured. The position of the proton in these two series of salts is uncertain. In the benzimidazole series (VIII), the marked difference in colour between the salt and the base indicates that the proton has probably not united with the azomethine-nitrogen atom: if it united with a ring-nitrogen atom of the imidazole, the positive charge could be shared between this and the azomethine nitrogen atom with the probable production of colour. In the quinazoline series (IV), the difference in colour between the salt and the base is less marked, and the proton may have united with the azomethine-nitrogen atom: alternatively it could be united with the $N_{(12)}$ atom, in which case the positive charge could be shared between these two nitrogen atoms, thus again producing a cyanine type of salt.

The diazonium derivatives of the benzimidazoquinazoline (IV; R = *o*-C_6H_4·NH_2) proved to be of considerable interest. A solution of this amine in hydrochloric acid, when treated at 0° with nitrous acid, gave the diazonium chloride (IX), which had normal properties; for example, with alkaline 2-naphthol it gave the deep red crystalline azo-derivative (X). The aqueous solution of the chloride (IX), when added to cold saturated aqueous sodium hydrogen carbonate, deposited 3-[*o*-(benzimidazol-2-yl)phenyl]-1,2,3-benzotriazin-4-one (XI), pale yellow needles, m. p. 254°. It appeared probable that this compound would show considerable hydrogen-bonding between the :CO and the :NH

[3] Zentmyer and Wagner, *J. Org. Chem.*, 1949, **14**, 967.

group, and that this process might even be succeeded by definite cyclisation to the hydroxy-compound (XII). The structure (XI) was confirmed, however, by the infrared spectrum, which showed marked bands at 3190 and 1660 cm.$^{-1}$, indicating the :NH and :CO groups, respectively, but no band corresponding to an ·OH group. The structure was further confirmed by the formation of the compound (XI) in high yield by the action of hydrogen carbonate on a solution of the diazotised benzimidazole (II; R = *o*-C_6H_4·NH_2). Treatment of the compound (XI) with concentrated hydrochloric acid did not regenerate the diazonium chloride (IX).



a, HCl/HNO_2; *b*, 2-HO·$C_{10}H_7$/NaOH; *c*, $NaHCO_3$; *d*, HNO_2; *e*, NaOH aq.; *f*, Ac_2O; *g*, AcOH; *h*, 2-HO·$C_{10}H_7$ (fused); *i*, Me_2CO + acid.

Treatment of the above 1,2,3-benzotriazin-4-one (XI), or the diazonium chloride (XI), with aqueous sodium hydroxide gave an intensely yellow solution which, when saturated with solid sodium chloride, yielded yellow needles of the sodium salt of 2-[*o*-(*o*-carboxyphenyl)diazoaminophenyl]benzimidazole (XIII). This compound could be readily recrystallised from aqueous acetone, and was then obtained as a tetrahydrate.

When this sodium salt (XIII) was gently warmed with acetic anhydride, it was reconverted into the 1,2,3-benzotriazin-4-one (XI). When treated with hot acetic acid, or with hot mineral acids, the sodium salt (XIII) decomposed to yield anthranilic acid (as a salt) and benzimidazo[1,2-*c*][1,2,3]benzotriazine (XIV). More vigorous acid treatment of the latter compound (XIV) yielded nitrogen and 2-*o*-hydroxyphenylbenzimidazole, as von Niementowski has recorded.[4]

An attempt to isolate the free acid corresponding to the sodium salt (XIII) was not successful, the product being too unstable for characterisation. It appeared to decompose readily to anthranilic acid and the benzimidazobenzotriazine (XIV).

Gentle fusion of the sodium salt (XIII) with 2-naphthol yielded the azo-2-naphthol derivative (XV), which was also obtained when the triazine (XIV) was similarly treated.

The benzimidazoquinazoline (IV; R = *o*-C_6H_4·NH_2) was not readily methylated, and after 8 hours' boiling with ethanolic methyl iodide only the monomethylamino-compound

[4] von Niementowski, *Ber.*, 1897, **30**, 3062; 1898, **31**, 314; 1899, **32**, 1456.

(IV; R = *o*-C_6H_4·NHMe) was obtained: the amine was unaffected by the use of methanolic methyl iodide or of the iodide alone under these conditions. This inability of the amino-group to undergo further methylation, presumably because of steric obstruction, was confirmed by heating the primary amine with an excess of methyl toluene-*p*-sulphonate at 180° for 4 hours: even under these vigorous conditions the amino-group again underwent solely monomethylation, and one of the imidazole-nitrogen atoms underwent quaternisation. When the resulting salt was treated in cold aqueous solution with sodium hydroxide, the pyrimidine ring opened, giving 1-methyl-2-[*o*-(*o*-methylamino)benzamidophenyl]-benzimidazole. This compound was identified by (*a*) analysis, (*b*) the formation of acetyl and nitrosamine derivatives, and (*c*) its infrared spectrum, which showed strong, sharp bands at 1675 and 3500 cm.$^{-1}$, characteristic of the :CO and ·NH· groups of an acid amide, confirmed by an " amide-II " band of a secondary amide at 1525 cm.$^{-1}$: moreover, if the $N_{(5)}$ group of the amine (IV; R = *o*-C_6H_4·NH_2) had undergone quaternisation, giving the ·CO·NMe· group in the final product, the band given by the NMe portion of this group would probably have been in the 3300—3200 cm.$^{-1}$ region owing to intramolecular hydrogen bonding of the :CO and the imidazole ·NH· groups.

Experimental

All compounds were colourless unless otherwise described.

2-*o*-Aminophenylbenzimidazole (I), m. p. 213—214° (lit.,[5] 213—214°), was prepared by condensation of *o*-phenylenediamine and anthranilic acid in the presence of polyphosphoric acid, as described by Hein *et al.*[5]

The amino-compound (I) (2 g.) and 2-methyl-3,1-benzoxazin-4-one (acetanthranil) [6] (VI; R = Me) were gently fused together for 10 min. The crude product, after repeated recrystallisation from aqueous ethanol, yielded 6-methylbenzimidazo[1,2-*c*]quinazoline (IV; R = Me), (1·2 g.), needles, m. p. and mixed m. p. 176–177° (lit.,[4] 177°).

2-[o-(o-*Nitrobenzamido*)*phenyl*]*benzimidazole* (II; R = *o*-C_6H_4·NO_2).—*o*-Nitrobenzoyl chloride (20 g., 1·1 mol.) was added dropwise during 30 min. to a stirred solution of the amino-compound (I) (20 g.) in dry pyridine (100 c.c.), and the mixture was then heated on a water-bath for 30 min. It was cooled and poured slowly into stirred ice–water mixture (*ca.* 500 g.) containing ammonia solution (*d* 0·880; 20 c.c.). After 2 hours' stirring, the yellow solid was collected, washed with water, and dried: for purification it was dissolved in hot dimethylformamide (100 c.c.), which was shaken with charcoal (2—3 g.), filtered, reheated, and diluted with boiling water (80—100 c.c.), and cooled. The *nitro-compound* (II; R = *o*-C_6H_4·NO_2) separated as pale yellow needles (35 g., 93%), m. p. 251° (Found: C, 66·9; H, 3·8; N, 15·3. $C_{20}H_{14}N_4O_3$ requires C, 67·0; H, 3·9; N, 15·6%).

A similar preparation, with a solution of the (solid) *p*-nitrobenzoyl chloride in a small volume of tetrahydrofuran, afforded the p-*nitro-compound* (II; R = *p*-C_6H_4·NO_2) (75%), forming from dimethylformamide yellow needles, m. p. 335° (Found: C, 67·3; H, 3·7; N, 16·0. $C_{20}H_{14}N_4O_3$ requires C, 67·0; H, 3·9; N, 15·6%).

2-[o-(o-*Aminobenzamido*)*phenyl*]*benzimidazole* (II; R = *o*-C_6H_4·NH_2).—Ethanol (150 c.c.) and zinc dust (250 g.) were added to a stirred solution of the nitro-compound (II; R = *o*-C_6H_4·NO_2) (40 g.) in dry pyridine (250 c.c.), to which acetic acid (45 c.c.) was then added slowly, the mixture being cooled meanwhile with ice-water. The complete mixture was stirred for 15 min. and then filtered, the residual zinc being washed on the filter with pyridine (2 × 50 c.c.). The combined filtrates were heated to boiling and then diluted with an equal volume of boiling water containing ammonia solution (*d* 0·880; 40 c.c.). The *amino-compound* (II; R = *o*-C_6H_4·NH_2) rapidly separated as needles (25 g., 68%), m. p. 257°, after collection, washing with water, ethanol, and ether and drying (Found: C, 72·8; H, 5·0; N, 17·3. $C_{20}H_{16}N_4O$ requires C, 73·1; H, 4·9; N, 17·1%).

The corresponding p-*amino-compound* (II; R = *p*-C_6H_4·NH_2), similarly prepared in 80% yield, formed hair-like needles, m. p. 254—256° (Found: C, 73·1; H, 5·1; N, 17·4%).

A suspension of the *o*-amino-compound (II; R = *o*-C_6H_4·NH_2) in an excess of acetic

[5] Hein, Alheim, and Leavitt, *J. Amer. Chem. Soc.*, 1957, **79**, 427.
[6] Bogert and Seil, *J. Amer. Chem. Soc.*, 1907, **29**, 517.

anhydride, when set aside overnight, deposited the o-*acetamido-derivative* (II; R = *o*-C_6H_4·NHAc), which when collected, washed with water, and recrystallised from aqueous pyridine, formed needles, m. p. 297° (decomp.), in almost quantitative yield (Found: C, 71·7; H, 5·0; N, 15·4. $C_{22}H_{18}N_4O_2$ requires C, 71·3; H, 4·9; N, 15·1%). The o-*benzamido-derivative* (II; R = *o*-C_6H_4·NHBz) formed crystals, m. p. 245—246°, from aqueous pyridine (Found: C, 75·4; H, 4·9; N, 13·2. $C_{27}H_{20}N_4O_2$ requires C, 75·15; H, 4·7; N, 13·0%).

2-o-(2-*Methylquinazol*-4-*on*-3-*yl*)*phenylbenzimidazole* (III).—The *o*-acetamido-compound (II; R = *o*-C_6H_4·NHAc), when heated at 300°/15 mm., gave a sublimate of the *compound* (III), prisms, m. p. 300° (from ethanol) (Found: C, 75·2; H, 4·9; N, 15·9. $C_{22}H_{16}N_4O$ requires C, 75·0; H, 4·6; N, 15·9%). When a toluene solution of equimolecular quantities of the *o*-acetamido-compound and phosphoryl chloride was boiled under reflux for 1 hr. and cooled, the compound (III) was deposited, having m. p. and mixed m. p. 300° after crystallisation from ethanol.

2-o-*Benzylideneaminophenylbenzimidazoles* (V).—Several members of this class (Table 1)

TABLE 1.

2-*o*-(*o*-, *m*-, or *p*-Substituted benzylideneamino)phenylbenzimidazoles (V).

			Found (%)				Required (%)		
R	M. p.	Yield (%)	C	H	N	Formula	C	H	N
C_6H_5	222° *a*	97	80·8	5·3	14·4	$C_{20}H_{15}N_3$	80·8	5·1	14·1
o-C_6H_4·NO_2 ...	259 *b*	95	70·3	3·9	16·5	$C_{20}H_{14}N_4O_2$	70·2	4·1	16·4
m- ,, ...	235 *c*	82	70·3	4·3	16·6	,,	,,	,,	,,
p- ,, ...	223 *b*	77	70·2	3·9	16·7	,,	,,	,,	,,
o-C_6H_4·NH_2 ...	211 *c*	80	76·8	5·4	18·2	$C_{20}H_{16}N_4$	76·9	5·1	18·0
o-C_6H_4·OH ...	289 *b*	89	76·5	5·0	13·8	$C_{20}H_{15}N_3O$	76·7	4·8	13·4
m- ,, ...	320 *b*	93	76·3	4·2	13·7	,,	,,	,,	,,
p- ,, ...	318 *b*	91	76·55	5·2	13·55	,,	,,	,,	,,
o-C_6H_4·CO_2H...	231 *a*	70	74·2	4·7	12·5	$C_{21}H_{14}N_3O_2$	73·9	4·4	12·3

a, From propan-1-ol. *b*, From aqueous pyridine. *c*, From aqueous dimethylformamide.

TABLE 2.

6-(*o*-, *m*-, or *p*-Substituted phenyl)benzimidazo[1,2-*c*]quinazolines (IV).

			Found (%)				Required (%)		
R	M. p.	Yield (%)	C	H	N	Formula	C	H	N
C_6H_5	242° * *a*	82	81·3	4·3	14·3	$C_{20}H_{13}N_3$	81·3	4·4	14·2
o-C_6H_4·NO_2...	211·5 *b*	84	70·6	3·6	16·7	$C_{20}H_{12}N_4O_2$	70·6	3·6	16·5
m- ,, ...	265 *c*	70	70·6	3·9	16·7	,,	,,	,,	,,
p- ,, ...	261 *c*	70	70·8	3·4	16·6	,,	,,	,,	,,
o-C_6H_4·NH_2...	267—268 *c*	70	77·1	4·7	18·3	$C_{20}H_{14}N_4$	77·4	4·6	18·05
o-C_6H_4·OH ...	300 *c*	63	76·9	4·7	14·1	$C_{20}H_{13}N_3O$	77·2	4·2	13·5
m- ,, ...	317 *c*	45	77·1	5·1	13·7	,,	,,	,,	,,
p- ,, ...	344 *c*	50	76·6	4·1	14·1	,,	,,	,,	,,
o-C_6H_4·CO_2H	303 *a*	70	74·0	4·2	12·2	$C_{21}H_{13}N_3O_2$	74·3	3·9	12·4

a—*c*, See Table 1. * Lit.,[4] 239°.

were prepared to investigate the general application of the oxidative cyclisation to corresponding compounds of type (IV) (Table 2). They were prepared by adding in turn the aldehyde (1·1 mol.) and acetic acid (2—3 drops) to a hot solution of the amine (I) in *ca.* 10 parts of boiling propan-1-ol, which was then heated under reflux for 5—10 min. *o*-Aminobenzaldehyde required longer heating (1½ hr.). After cooling, the azomethine (V) was collected, washed with propanol, and recrystallised as indicated above. An azomethine was not obtained from *p*-dimethylaminobenzaldehyde.

All the members tabulated are new, and all are colourless, except the *o*-, *m*-, and *p*-nitrophenyl compounds, which are orange-red, yellow-orange, and deep yellow, respectively.

Thermal Decomposition of the p-*Hydroxybenzylidene Compound* (V; R = *p*-C_6H_4·OH).—This compound (0·6 g.), when heated at 330°, melted and effervesced briskly. After 5 min., the residue was powdered and extracted with 10% aqueous sodium hydroxide solution (1·25

c.c.). The filtered extract, when treated with toluene-*p*-sulphonyl chloride, yielded phenyl toluene-*p*-sulphonate, m. p. and mixed m. p. 96° (from ethanol). The residue, after recrystallisation from ethanol, yielded the parent benzimidazo[1,2-*c*]quinazoline (IV; R = H), m. p. and mixed m. p. 229° (lit.,[4] 227°).

6-o-*Aminophenylbenzimidazo*[1,2-*c*]*quinazoline* (IV; R = *o*-C_6H_4·NH_2).—(A) *From the benzamido-compound* (II; R = *o*-C_6H_4·NH_2). (i) This compound when heated at 280°/15 mm., melted, and the *quinazoline* (IV; R = *o*-C_6H_4·NH_2) appeared in the upper cooler part of the tube as long needles, m. p. 267—268° after recrystallisation from aqueous dimethylformamide, (Found: C, 77·1; H, 4·7; N, 18·3. $C_{20}H_{14}N_4$ requires C, 77·4; H, 4·6; N, 18·05%).

(ii) The benzamido-compound (II; R = *o*-C_6H_4·NH_2) (0·3 g.), dissolved in pyridine (15 c.c.), was heated with phosphorus pentoxide (1·5 g.) under reflux for 1½ hr. The mixture was cooled, filtered, and diluted with water (*ca.* 50 c.c.), the quinazoline (IV; R = *o*-$C_6H_4NH_2$) (0·1 g.) slowly crystallising: it had m. p. 267—268° after recrystallisation as before.

(iii) A mixture of the compound (II; R = *o*-C_6H_4·NH_2) (25 g.) and polyphosphoric acid (250 g.) was heated with stirring to 250°, kept at this temperature for 30 min., cooled, and poured slowly into water–ice (*ca.* 3 l.). The solution was basified with aqueous ammonia (*d* 0·880) and set aside overnight, and the precipitated quinazoline (IV; R = *o*-$C_6H_4NH_2$) then collected. It was recrystallised from a hot, filtered solution in dimethylformamide, to which water had been cautiously added, giving needles (14 g., 60%) m. p. 267—268°. For large-scale work, this method of cyclisation is greatly superior to methods (i) and (ii).

(B) *From the* o-*aminobenzylidene compound* (V; R = *o*-C_6H_4·NH_2). This and other substituted benzylidene compounds (Table 1) were oxidised by the following general method.

Powdered potassium permanganate (*ca.* 1·5 equiv.) was added to a solution of the benzylidene compound (V) in acetone (*ca.* 50 parts), and the mixture boiled under reflux for 15 min. It was then filtered hot, and an equal volume of hot water added to the filtrate. The quinazoline (IV) rapidly separated, and was collected and recrystallised as indicated above.

In view of the long preparation and general instability of *o*-aminobenzaldehyde, method (A), with intermediate isolation of the compound (II; R = *o*-C_6H_4·NH_2), provides the most convenient larger-scale preparation of the 6-aminoquinazoline (IV; R = *o*-C_6H_4·NH_2).

The tabulated benzimidazoquinazolines (IV), with the exception of the first, are new; all are colourless except the bright yellow *o*-nitrophenyl compound and the pale yellow *m*- and *p*-nitrophenyl compounds.

(C) 2-*o*-Nitrophenyl-3,1-benzoxazin-4-one (VI; R = *o*-C_6H_4·NO_2) was prepared by Zentmyer and Wagner's method.[3] A mixture of this compound (0·96 g.) and *o*-phenylenediamine (0·36 g.) was heated to 220° for 30 min. Repeated extraction of the cooled, powdered product with acetone finally yielded a small residue which, on recrystallisation from ethanol, gave the benzimidazole (II; R = *o*-C_6H_4·NO_2), m. p. and mixed m. p. 251°. The combined acetone extracts were evaporated, and the residue, when recrystallised from aqueous acetone, gave the quinazoline (IV; R = *o*-C_6H_4·NO_2) (*ca.* 0·02 g.), m. p. and mixed m. p. 211·5°.

(D) *From the* o-*nitrophenyl compound* (IV; R = *o*-C_6H_4·NO_2). The nitro-compound (IV; R = *o*-C_6H_4·NO_2) (1 g.) was reduced by the pyridine–zinc dust method (above), and gave an impure product, from which the pure *o*-aminophenyl compound (IV; R = *o*-C_6H_4·NH_2) (*ca.* 0·05 g.) was obtained by repeated recrystallisation from aqueous dimethylformamide. Other methods of reduction gave even lower yields of the amino-compound.

6-o-*Acetamidophenylbenzimidazole*[1,2-c]*quinazoline* (IV; R = *o*-C_6H_4·NHAc).—The amino-compound (IV; R = *o*-C_6H_4·NH_2) (1·0 g.) was dissolved in pyridine (10 c.c.) and acetic anhydride (0·5 c.c.) added. The mixture was heated under reflux for 1 hr., then hot water (25 c.c.) was added. When cool, the *acetamido-compound* was collected, dried, and recrystallised from aqueous pyridine, yielding needles, m. p. 237° (0·92 g., 85%) (Found: C, 74·7; H, 4·6; N, 16·0. $C_{22}H_{16}N_4O$ requires C, 75·0; H, 4·6; N, 15·9%). It gave a *hydrochloride*, m. p. 263° (Found: C, 68·3; H, 4·4; N, 14·7. $C_{22}H_{16}N_4O$,HCl requires C, 67·95; H, 4·4; N, 14·4%), and a yellow *picrate*, m. p. 251° (decomp.) (from ethanol) (dried at 100°/0·1 mm.) (Found: C, 57·5; H, 3·8; N, 17·1. $C_{22}H_{16}N_4O$,$C_6H_3N_3O_7$ requires C, 57·8; H, 3·5; N, 16·9%).

The o-*formamidophenyl* compound (IV; R = *o*-C_6H_4·NH·CHO), recrystallised from aqueous-ethanolic dimethylformamide, had m. p. 305—306° (Found: C, 74·4; H, 4·2; N, 16·7. $C_{21}H_{14}N_4O$ requires C, 74·5; H, 4·2; N, 16·6%).

The p-*aminophenyl compound* (IV; R = *p*-C_6H_4·NH_2) was prepared from the *p*-amino-compound (II; R = *p*-C_6H_4·NH_2) by method (A)(i) above: it formed needles, m. p. 290—

290·5°, from aqueous pyridine (Found: C, 77·0; H, 4·6; N, 17·8. $C_{20}H_{14}N_4$ requires C, 77·4; H, 4·6; N, 18·05%).

Attempted Preparation of Salts of Type (VII).—The acetyl compound (IV; R = *o*-C_6H_4·NHAc) was treated with (i) dilute mineral acids, (ii) concentrated hydrochloric acid, (iii) hydrogen chloride in boiling ethanol, (iv) perchloric acid in acetic acid, but in no case was a salt of type (VII) isolated; the action of the acid was merely to hydrolyse the acetamido-group.

Attempted Preparation of the 6-o-*Thioacetamidophenyl Derivative* (IV; R = *o*-C_6H_4·NH·CSMe)—(1) The acetyl compound (IV; R = *o*-C_6H_4·NHAc) (0·27 g.) was dissolved in boiling toluene (25 c.c.), and phosphorus pentasulphide (0·19 g., 1·1 mol.) added.[7] The mixture was heated under reflux for 1½ hr., then cooled, and the bright yellow product (0·28 g.) which had separated was collected and dried. It had an indefinite m. p., *ca.* 276° (decomp.), but could not be satisfactorily purified. It appeared to be an approximately equimolecular mixture of the acetyl compound and phosphorus pentasulphide (Found: C, 48·5; H, 3·6; N, 9·7. Calc. for $C_{22}H_{16}N_4O,P_2S_5$: C, 46·0; H, 2·8; N, 9·8%).

(2) The amino-compound (IV; R = *o*-C_6H_4·NH_2), dissolved in methanol, was treated with methanolic methyl dithioacetate.[8] No reaction occurred either in the cold or on warming.

Attempted Preparation of the 6-o-*Thioformamidophenyl Derivative* (IV; R = *o*-C_6H_4·NH·CSH)—The amino-compound (IV; R = *o*-C_6H_4·NH_2), dissolved in dilute hydrochloric acid, was treated with an excess of sodium dithioformate.[9] No recognisable product could be isolated from the mixture.

2-o-*Isopropylideneaminophenylbenzimidazole* (VIII; R = R′ = Me).—Acetone (1 c.c.) and aqueous hydriodic acid of constant b. p. (1 c.c.) were added to a boiling solution of the amine (I) (1·0 g.) in ethanol (25 c.c.). The solution was cooled and the yellowish-green crystals (1·5 g., 83%) of the *hydriodide* of the base, when collected and recrystallised from ethanol, had m. p. 262° (Found: C, 50·5; H, 4·2; N, 11·3. $C_{16}H_{15}N_3$,HI requires C, 50·9; H, 4·3; N, 11·1%). This salt, when treated in ethanolic solution with aqueous sodium hydroxide, deposited the *base* (VIII; R = R′ = Me), needles, m. p. 262° (from ethanol) (Found: C, 77·1; H, 6·1; N, 16·9. $C_{16}H_{15}N_3$ requires C, 77·1; H, 6·1; N, 16·9%). Solutions of the base showed only a very slight fluorescence, in contrast to that of solutions of the hydriodide. An acetone solution of the base, treated with aqueous picric acid, deposited the *picrate*, yellow needles, m. p. 219—220° (from aqueous acetone) (Found: C, 55·5; H, 3·9; N, 17·8. $C_{16}H_{15}N_3,C_6H_3N_3O_7$ requires C, 55·2; H, 3·8; N, 17·6%).

Ethyl methyl ketone (0·72 g.) was added to a boiling solution of the amine (I) (2·09 g., 1 mol.) in ethanol (30 c.c.), and a rapid stream of dry hydrogen chloride passed through the mixture. The solution, which displayed a brilliant green fluorescence, was cooled and diluted with ether (35 c.c.). The *hydrochloride* of the 2-*o*-s-butylideneaminophenyl base (VIII; R = Me, R′ = Et) separated as yellow needles, m. p. 230°, from ethanol–ether (Found: C, 67·9; H, 6·3; N, 13·7. $C_{17}H_{17}N_3$,HCl requires C, 68·1; H, 6·1; N, 14·0%).

6-o-*Isopropylideneaminophenylbenzimidazo*[1,2-*c*]*quinazoline* (IV; R = *o*-C_6H_4·N:CMe_2).—Hydriodic acid (2—3 drops) was added to a solution of the quinazoline (IV; R = *o*-C_6H_4·NH_2) (0·15 g.) in acetone (10 c.c.), which was boiled under reflux for 5 min. The solution, when cooled and diluted with ether (15 c.c.), deposited the *hydriodide* of the base (IV; R = *o*-C_6H_4·N:CMe_2), very pale yellow needles, m. p. 358° (decomp.) (Found: C, 58·1; H, 4·3; N, 11·6. $C_{23}H_{18}N_4$,HI requires C, 57·8; H, 4·0; N, 11·7%). When in this experiment the hydriodic acid was replaced by methyl iodide (2 c.c.), with boiling for 4 hr., the salt was similarly obtained.

The hydriodide, when treated in ethanolic solution with aqueous sodium hydroxide deposited the *base* (IV; R = *o*-C_6H_4·N:CMe_2), cream-coloured crystals, m. p. 323° (from aqueous pyridine) (Found: C, 78·6; H, 5·7; N, 16·1. $C_{23}H_{18}N_4$ requires C, 78·8; H, 5·2; N, 16·0%).

Diazotisation of 6-o-*aminophenylbenzimidazo*[1,2-*c*]*quinazoline* (IV; R = *o*-C_6H_4·NH_2).—A suspension of the quinazoline (1·4 g.) in a mixture of water (50 c.c.) and concentrated hydrochloric acid (5 c.c.) was cooled to 0°, and stirred whilst sodium nitrite (0·35 g., 1·1 mol.) in water (5 c.c.) was added dropwise, the clear solution being stirred for a further 30 min.

A portion of this solution, when added to an alkaline solution of 2-naphthol, deposited 6-[o-(2-*hydroxy*-1-*naphthylazo*)*phenyl*]*benzimidazo*[1,2-*c*]*quinazoline* (X), deep red crystals,

[7] Kindler, *Annalen*, 1923, **431**, 207.
[8] Peak and Stansfield, *J.*, 1952, 4067.
[9] Todd, Bergel, Karimullah, and Kelling, *J.*, 1937, 361.

m. p. 260—262° (from ethanol) (Found: C, 77·5; H, 4·5; N, 14·9. $C_{30}H_{19}N_5O$ requires C, 77·4; H, 4·1; N, 15·0%).

3-[o-(*Benzimidazol-2-yl*)*phenyl*]-1,2,3-*benzotriazin-4-one* (XI).—(A) A portion of the above diazonium solution was poured into an excess of aqueous sodium hydrogen carbonate solution, giving a cream-coloured precipitate, which when collected, washed with water, and recrystallised from aqueous acetone gave the *triazine* (XI) (65% calculated on the amine employed), pale yellow needles, m. p. 254° (decomp.) (Found: C, 70·9; H, 3·7; N, 20·6. $C_{20}H_{13}N_5O$ requires C, 70·8; H, 3·8; N, 20·6%). It gave a *picrate*, pale yellow needles, m. p. 196° (decomp.), from aqueous acetone (Found: C, 55·4; H, 3·2; N, 19·5. $C_{20}H_{13}N_5O,C_6H_3N_3O_7$ requires C, 55·0; H, 2·8; N, 19·5%).

(B) 2-[*o*-(*o*-Aminobenzamido)phenyl]benzimidazole (II; R = *o*-$C_6H_4{\cdot}NH_2$) was diazotised precisely as the above quinazoline (IV; R = *o*-$C_6H_4{\cdot}NH_2$). The clear diazonium solution, when added to the carbonate solution, also gave the triazinone (XI) (92% calculated on the amine used), m. p. and mixed m. p. 254° (decomp.). This route provides the shortest and best synthesis of the compound (XI).

It is noteworthy that neither the solution of the diazotised amine (II; R = *o*-$C_6H_4{\cdot}NH_2$) nor a solution of the triazinone (XI) in concentrated hydrochloric acid gave an azo-compound when added to an alkaline solution of 2-naphthol.

Sodium Salt of 2-[o-(o-*Carboxyphenyl*)*diazoaminophenyl*]*benzimidazole* (XIII).—25% Aqueous sodium hydroxide (4 c.c.), when added to a suspension of the oxotriazine (XI) (0·95 g.) in ethanol (10 c.c.), gave a deep yellow solution, which was diluted with water (20 c.c.), heated to boiling, and then almost saturated with sodium chloride. On cooling, the solution deposited the *sodium salt tetrahydrate*, bright yellow needles (1·1 g., 83%), m. p. 180° (decomp.) after being washed with a small quantity of water, and recrystallised from aqueous acetone (Found: Na, 4·7; H_2O, 16·0. $C_{20}H_{14}N_5NaO_2,4H_2O$ requires Na, 5·1; H_2O, 16·0%). When heated at 125°/0·2 mm. for 8 hr., it gave the anhydrous *salt* (XIII) with unchanged m. p. (Found: C, 61·1; H, 3·9; N, 18·5. $C_{20}H_{14}N_5NaO_2$ requires C, 61·7; H, 3·7; N, 18·5%).

Reactions of the Sodium Salt (XIII).—(1) A mixture of the salt (0·1 g.) and acetic anhydride (1 c.c.), when warmed very gently and then cooled, deposited the oxotriazine (XI), m. p. 254° (decomp.) (from aqueous acetone).

(2) A mixture of the salt (0·1 g.) and 50% w/w sulphuric acid (2 c.c.) was heated at *ca.* 100° for 10 min., the yellow colour being replaced by pale pink. On cooling, the solution deposited colourless needles of anthranilic acid hydrogen sulphate, m. p. and mixed m. p. 189°. A similar mixture with 80% sulphuric acid, when heated to boiling for a few min. and then cooled and diluted with water, deposited sulphanilic acid.

(3) A mixture of the salt (0·1 g.) and acetic acid (2 c.c.), when heated to boiling, cooled, and diluted with water, deposited the pale yellow benzimidazo[1,2-*c*][1,2,3]benzotriazine (XIV), m. p. 211° (lit.,[4] 211°) (from aqueous pyridine). Admixture with an authentic sample, prepared by the action of nitrous acid on the benzimidazole (I), did not affect the m. p.

(4) In an attempt to isolate the free acid from its sodium salt, dilute acetic acid was added dropwise to a solution of the salt (0·1 g.) in water (20 c.c.). The precipitated yellow acid was rapidly collected and dried; it had an indefinite m. p., *ca.* 140° (decomp.), Although this product was initially insoluble in chloroform, exposure to the air for a few hr. caused partial decomposition with the formation of the above triazine (XIV), which was extracted with cold chloroform and had m. p. and mixed m. p. 211° after crystallisation from aqueous pyridine. Attempts to isolate the unstable acid were therefore abandoned.

(5) A mixture of the salt (0·1 g.) and 2-naphthol (0·1 g.) when fused gently together produced 2-[o-(2-*hydroxy*-1-*naphthylazo*)*phenyl*]*benzimidazole* (XV) as crimson needles, m. p. 261° (from aqueous ethanol) (Found: C, 75·1; H, 4·6; N, 15·7. $C_{23}H_{16}N_4O$ requires C, 75·6; H, 4·4; N, 15·4%). The identity of this compound was confirmed by its formation when benzimidazo[1,2-*c*][1,2,3]benzotriazine (XIV) was similarly fused with 2-naphthol.

Methylation of the Amino-compound (IV; R = *o*-$C_6H_4{\cdot}NH_2$).—(1) A solution of the amine (0·5 g.) in ethanol (10 c.c.) and methyl iodide (3 c.c.), when boiled under reflux for 8 hr. and cooled, deposited the *monomethylamine* (IV; R = *o*-$C_6H_4{\cdot}NHMe$) (0·2 g., 38%), needles, m. p. 288° (from aqueous dimethylformamide) (Found: C, 77·4; H, 5·0; N, 17·8. $C_{21}H_{16}N_4$ requires C, 77·7; H, 5·0; N, 17·3%). It gave a *picrate*, yellow crystals, m. p. 228° (decomp.) (from ethanolic dimethylformamide) (Found: N, 18·0. $C_{21}H_{16}N_4,C_6H_3N_3O_7$ requires N, 17·7%).

(2) A mixture of the amine (0·25 g.) and methyl toluene-*p*-sulphonate (0·5 g.) was heated at 180° for 4 hr. The brown syrupy product was extracted with cold ether to remove the excess of the ester, and the viscous residue, when dissolved in water and treated with aqueous sodium hydroxide, deposited 1-*methyl*-2-[o-(o-*methylamino*)*benzamidophenyl*]*benzimidazole*, m. p. 228° (after recrystallisation from ethanol and drying at 80°/0·1 mm.) (Found: C, 74·4; H, 6·05; N, 15·7. $C_{22}H_{20}N_4O$ requires C, 74·2; H, 5·64; N, 15·7%). This compound, treated with acetic anhydride–pyridine, gave a very hygroscopic acetyl derivative, which rapidly became yellow on exposure to air and colourless again on renewed dehydration: it had m. p. 198° after crystallisation from aqueous dimethylformamide. The compound also gave a pale yellow nitrosamine, m. p. 188° (decomp.) (from aqueous pyridine): it gave a strong Liebermann's colour reaction. The quantities available of each of these recrystallised derivatives were insufficient for accurate analysis.

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