421. *Some New Benziminazole Derivatives.*

By P. R. Thomas and G. J. Tyler.

A synthesis of benziminazoles from imidoate hydrochlorides and *o*-phenylenediamines described by King and Acheson [1] is of particular value for the preparation of 2-arylbenziminazoles. For 2-alkyl derivatives it is not so useful when the *o*-diamine possesses an electrophilic substituent in the 4-position.

King and Acheson [1] have prepared numerous 2-alkylbenziminazoles by reaction of *o*-phenylenediamines with alkyl imidoate hydrochlorides in methanol. This method has now been applied to the synthesis of some 2-arylbenziminazoles, in preference to others [2] because, in general, it gave higher yields of purer products. Weidenhagen's method [3]

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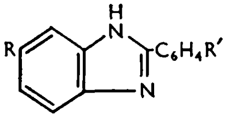
[1] King and Acheson, *J.*, 1949, 1396.

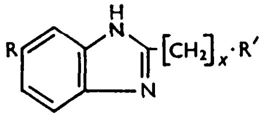
[2] Partridge and Turner, *J. Pharm. Pharmacol.*, 1953, **5**, 114; Hölljes and Wagner, *J. Org. Chem.*, 1944, **9**, 43; Porai-Koshits *et al.*, *J. Gen. Chem. U.S.S.R.*, 1947, **17**, 1768; 1949, **19**, 1545.

[3] Weidenhagen, *Ber.*, 1936, **69**, 2263; 1942, **75**, 1936.

whereby *o*-phenylenediamines and aromatic aldehydes are condensed in the presence of cuprous acetate uses relatively inaccessible aldehydes and gives lower yields. We thus prepared the benziminazoles (I) in which R = R′ = H (83%), Me (81%), and CO_2Me (92%) and the bisiminazoles (III; $x = 4$ and 8).[4]



(I)



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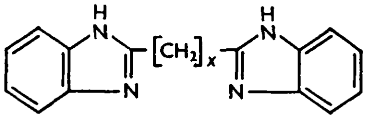

(III)

Where the *o*-diamine carried an electrophilic substituent, *e.g.*, 4-NO_2 or 4-CO_2Me, it reacted with difficulty and gave a low yield of benziminazole. By this method small quantities of 2-(ω-carboxy-*n*-octyl)-5-methoxycarbonylbenziminazole (II; R = CO_2Me, R′ = CO_2H, $x = 8$) and 2-(ω-carboxy-*n*-octyl)-5-nitrobenziminazole (II; R = NO_2, R′ = CO_2H, $x = 8$) were obtained but such derivatives were better prepared by condensing the *o*-phenylenediamine derivative with excess of the carboxylic acid in 4N-hydrochloric acid.[5]

Attempts to prepare 5-carboxy-2-*p*-carboxyphenylbenziminazole by oxidation of 5-methyl-2-*p*-tolylbenziminazole with alkaline permanganate or chromic acid gave low yields of an impure product. The corresponding dimethyl ester, however, was obtained in high yield by the imidoate method, and alkaline hydrolysis gave the very high-melting, insoluble diacid, which was characterised as its salts with hexamethylene- and decamethylene-diamine.

Of the intermediates, ethyl *p*-methoxycarbonylbenzimidoate hydrochloride was prepared from methyl *p*-cyanobenzoate by Pinner's method.[6] Methyl 3 : 4-diaminobenzoate was prepared from aceto-*p*-toluidide in five stages in an overall yield of about 40%; nitration [7] gave 4-acetamido-3-nitrotoluene which was oxidised in neutral permanganate [8] to 4-acetamido-3-nitrobenzoic acid; hydrolysis then gave the amino-acid which was esterified and hydrogenated to methyl 3 : 4-diaminobenzoate.

2-(ω-Carboxy-*n*-octyl)-5-nitrobenziminazole was prepared as its hydrate by the condensation of 4-nitro-*o*-phenylenediamine with a large excess of sebacic acid in 4N-hydrochloric acid solution. The benziminazole derivative was converted into its methyl ester, which on hydrogenation gave 5-amino-2-(ω-methoxycarbonyl-*n*-octyl)benziminazole (II; R = NH_2, R′ = CO_2Me, $x = 8$). After reaction of methyl 3 : 4-diaminobenzoate and excess of sebacic acid 5-carboxy-2-(ω-carboxy-*n*-octyl)benziminazole (II; R = R′ = CO_2H, $x = 8$) was obtained *via* its hydrochloride.

EXPERIMENTAL

Amine Equivalent.—The equivalents of benziminazole derivatives were determined in acetic acid by titration with perchloric acid in acetic acid, α-naphtholbenzein being used as indicator.

Ethyl Benzimidoate Hydrochlorides.—Hydrogen chloride was passed into a mixture of nitrile, absolute ethanol and, sometimes, benzene at 0—5° until at least the theoretical quantity had been absorbed. After 1—3 days the product had solidified and was filtered off, washed with ether, and dried. Details are in Table 1.

Benziminazoles prepared from Ethyl Imidoate Hydrochlorides.—Approx. equimolecular quantities of imidoate hydrochloride and aromatic *o*-diamine in methanol were heated under reflux for 1 hr., then cooled, and filtered, and the filtrate was evaporated to small bulk and poured into water. The product was filtered off and recrystallised.

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[4] Cf. Shriner and Upson, *J. Amer. Chem. Soc.*, 1941, **63**, 2277.

[5] Phillips, *J.*, 1928, 2395, 3131.

[6] Pinner, " Die Imidoaether und ihre Derivate," Verlag R. Oppenheimer, Berlin, 1892.

[7] Gattermann, *Ber.*, 1885, **18**, 1483.

[8] Ullmann and Mauthner, *Ber.*, 1903, **36**, 4032.

The reaction mixture containing 2-(ω-carboxy-*n*-octyl)-5-nitrobenziminazole was poured into sodium hydroxide solution, the insoluble unchanged diamine filtered off, and the filtrate acidified to give the crude product.

Details of conditions and *products* are in Table 2.

TABLE 1. *Preparation of ethyl imidoate hydrochlorides.*

Nitrile (g.)	EtOH (c.c.)	C_6H_6 (c.c.)	Product Formula [X = ·C(OEt)$\vdots$NH$_2$Cl]	Yield (%)
250	150	—	PhX	90
30	16	—	*p*-C_6H_4MeX	90
132	42	400	*p*-$CO_2Me{\cdot}C_6H_4X$	82
36·6	13	215	$HO_2C{\cdot}[CH_2]_8{\cdot}X$ *	52
54	70	300	$X{\cdot}[CH_2]_4{\cdot}X$	64
37·6	26	200	$X{\cdot}[CH_2]_8{\cdot}X$	68

* Solidified only when washed; slightly impure.

TABLE 2. *Some benziminazoles prepared from imidoate salts.*

No.	Diamine (g.)	Imidoate, HCl (g.)	MeOH (c.c.)	Product	Yield (%)	M. p.	Solvent for crystn.
1	180	280	1000	I; R = R′ = H	85	295°	MeOH
2	22·7 [b]	42	115	I; R = R′ = Me [a]	81	195	C_6H_6
3	25	38·6	500	I; R = R′ = CO_2Me	92	237	Dioxan
4	10·5	16·9	100	II; R = CO_2Me, R′ = CO_2H; *x* = 8 [c]	23	142—144	Aq. MeOH
5	5·6	9·84	50	II; R = NO_2, R′ = CO_2H; *x* = 8 [d]	19	104—107	Aq. $COMe_2$
6	5·0	6·3	40	III; *x* = 4	52	259	Aq. EtOH
7	21·6	32·9	150	III; *x* = 8	50	270	,,

	Found (%)				Found		Required (%)				Reqd.
No.	C	H	N	OMe	Amine equiv.	Formula	C	H	N	OMe	Amine equiv.
2	80·7	6·4	12·8	—	223	$C_{15}H_{14}N_2$	81·1	6·3	12·7	—	222
3	66·1	4·7	9·3	19·5	311	$C_{17}H_{14}O_4N_2$	65·8	4·5	9·1	19·9	310
4	64·8	7·0	8·9	10·1	333	$C_{18}H_{24}O_4N_2$	65·1	7·2	8·4	9·3	332
5	56·7	6·8	12·8	—	340	$C_{16}H_{21}O_4N_3,H_2O$	57·0	6·8	12·5	—	337
7	76·4	8·1	15·8	—	—	$C_{22}H_{26}N_4$	76·3	7·5	16·2	—	—

Footnotes to Table 2: (*a*) The *picrate* crystallised from alcohol as pale needles, m. p. 278—280° (decomp.) (Found: C, 56·2; H, 3·8; N, 15·0. $C_{21}H_{17}O_7N_5$ requires C, 55·9; H, 3·8; N, 15·5%). The *hydrochloride*, prepared by passing dry hydrogen chloride through a hot benzene solution of the base, had m. p. 290° (decomp.), and was easily hydrolysed by boiling water (Found: Cl, 13·8. $C_{15}H_{15}N_2Cl$ requires Cl, 13·7%).

This benziminazole was prepared by two further routes. (i) 3 : 4-Diaminotoluene (54 g.) and *p*-toluic acid (59·6 g.) were heated for 2 hr. at 180°, then boiled with 10% hydrochloric acid (500 c.c.) to remove unchanged diamine, and the insoluble product filtered off and boiled with 5% sodium hydroxide solution to remove unchanged acid. The residual solid was washed with water, dried and crystallised (charcoal) from benzene, giving 5-methyl-2-*p*-tolylbenziminazole as a grey solid (50% yield), m. p. 192—194°. (ii) 3 : 4-Diaminotoluene dihydrochloride (40 g.) and *p*-toluonitrile (22 g.) were heated at 180° for 3 hr. The product was extracted continuously with ether for 4 hr., dried, and boiled with 5% sodium hydroxide solution (250 c.c.). The product was filtered off, washed with water, and dried and then crystallised as before (50—60%; m. p. 193—194°).

(*b*) Distillation of the diamine followed by crystallisation from benzene–light petroleum gave an almost white product, m. p. 88—90°.

(*c*) The corresponding dicarboxylic acid was isolated thus. The oily product obtained from methyl 3 : 4-diaminobenzoate (50 g.) and ethyl ω-carboxynonanimidoate hydrochloride (85·9 g.) was extracted several times with ether to remove unchanged diamine. The residual oil was then hydrolysed with boiling 10% sodium hydroxide solution (500 c.c.) for 5 hr.

Neutralisation of the solution with acetic acid precipitated the crude *benziminazoledicarboxylic acid*. This was recrystallised twice from aqueous acetic acid and dried *in vacuo* at 80° for 16 hr. to decompose the unstable acetate, giving 5-carboxy-2-(ω-carboxy-*n*-octyl)benziminazole (31 g.), m. p. 223—225°.

(*d*) Isolated as monohydrate. The *methyl ester* was obtained (as straw-coloured needles, m. p. 124—125°) by esterification of 2-(ω-carboxy-*n*-octyl)-5-nitrobenziminazole with 5% methanolic hydrogen chloride (Found: C, 60·6; H, 6·7; N, 12·2; OMe, 9·1%; amine equiv., 335. $C_{17}H_{23}O_4N_3$ requires C, 61·2; H, 6·9; N, 12·6; OMe, 9·3%; amine equiv., 333): it did not form a hydrochloride.

2-p-*Carboxyphenylbenziminazole-5-carboxylic Acid* (I; R = R′ = CO_2H).—Methyl 2-(*p*-methoxycarbonylphenyl)benziminazole-5-carboxylate (18 g.) was boiled under reflux for 3 hr. with sodium hydroxide (4 g.) in ethanol (250 c.c.), then evaporated to dryness, and the residue was dissolved in water (100 c.c.). After filtration the solution was acidified with acetic acid. The solid *acid* was filtered off, washed with water, and dried (yield quantitative); it did not melt below 350° (Found: C, 64·0; H, 3·6; N, 10·0%; amine equiv., 279. $C_{15}H_{10}O_4N_2$ requires C, 63·8; H, 3·6; N, 9·9%; amine equiv., 282).

The acid (5 g.) was dissolved with warming in an aqueous solution (100 c.c.) of hexamethylenediamine (2·2 g.). After filtration, the solution was concentrated to 25 c.c. and cooled. The *salt* was filtered off, washed with methanol, and dried (5·2 g., 73%); it had m. p. 260—262° (Found: amine equiv., 135. $C_{21}H_{20}O_4N_4$ requires amine equiv., 133).

The *decamethylenediammonium salt* (70% yield), similarly obtained, melted at 213—216° (Found: amine equiv., 150. $C_{25}H_{34}O_4N_4$ requires amine equiv., 151).

5-*Amino-2-(ω-carboxy-*n*-octyl)benziminazole* (II; R = NH_2, R′ = CO_2H, $x = 8$).—2-(ω-Carboxy-*n*-octyl)-5-nitrobenziminazole (57 g.) was dissolved in boiling aqueous sodium hydroxide (37·5 g. in 400 c.c.). Sodium dithionite (hydrosulphite) (72 g.) was added in three portions. When the vigorous reaction had subsided, a solution of sodium hydroxide (30 g.) in water (120 c.c.) and sodium dithionite (72 g.) were added consecutively and the solution was boiled until almost colourless, then diluted to 1 l.; the *amino-acid*, precipitated by addition of hydrochloric acid, crystallised (charcoal) from aqueous ethanol (yield, 30 g.) (Found: amine equiv., 159. $C_{16}H_{23}O_2N_3,2H_2O$ requires amine equiv., 162·5). The hydrate was dried overnight at 50° *in vacuo*, giving the anhydrous *compound*, m. p. 140—143° (Found: amine equiv., 146. $C_{16}H_{23}O_2N_3$ requires amine equiv., 144·5).

5-*Amino-2-(ω-methoxycarbonyl-*n*-octyl)benziminazole* (II; R = NH_2, R′ = CO_2Me, $x = 8$).—(*a*) The foregoing acid dihydrate (21·7 g.) was boiled under reflux in 6% methanolic hydrogen chloride (250 c.c.) for 4 hr., then concentrated; the *ester dihydrochloride* crystallised; it was recrystallised from methanol (Found: C, 53·8; H, 6·5; N, 11·2; OMe, 8·0; Cl, 18·8. $C_{17}H_{27}O_2N_3Cl_2$ requires C, 54·2; H, 6·6; N, 11·1; OMe, 8·2; Cl, 18·9%). The free *ester*, obtained by treatment with warm sodium carbonate solution, recrystallised from benzene as pale pink plates (17·9 g.), m. p. 97—98° (Found: C, 66·9; H, 8·3; N, 13·9; OMe, 10·2%; amine equiv., 154. $C_{17}H_{25}O_2N_3$ requires C, 67·3; H, 8·2; N, 13 8; OMe, 10·2%; amine equiv., 152).

(*b*) 2-(ω-Methoxycarbonyl-*n*-octyl)-5-nitrobenziminazole (10 g.) was hydrogenated in ethyl acetate (200 c.c.) in the presence of 10% platinum–carbon (2 g.) at atmospheric pressure. When the theoretical quantity of hydrogen had been absorbed, the catalyst was filtered off and the filtrate evaporated to dryness. The residue on recrystallisation from benzene gave the 5-amine (8 g.), m. p. 97—98°.

The Phillips [5] procedure was employed for the synthesis of other benziminazolecarboxylic acids or their derivatives.

2-*(ω-Carboxy-*n*-octyl)-5-nitrobenziminazole* (II; R = NO_2, R′ = CO_2H, $x = 8$).—4-Nitro-*o*-phenylenediamine (100 g.) and sebacic acid (536 g.) were boiled under reflux in 4N-hydrochloric acid (3 l.) for 24 hr., then cooled, and the precipitate was filtered off, washed with water, and dried. Excess of sebacic acid was removed by continuous extraction with ether. The crude product was crystallised twice from aqueous acetone, yielding the monohydrate of 2-(ω-carboxy-*n*-octyl)-5-nitrobenziminazole as a pale yellow solid (78 g.), m. p. 105—108°.

5-*Carboxy-2-(ω-carboxy-*n*-octyl)benziminazole* (II; R = R′ = CO_2H, $x = 8$).—Methyl 3 : 4-diaminobenzoate (50 g.) and sebacic acid (240 g.) were boiled under reflux in 4N-hydrochloric acid (1500 c.c.) for 20 hr., then cooled and the precipitate was filtered off and then dried.

Continuous extraction with ether removed the excess of sebacic acid, leaving the hydrochloride of 5-carboxy-2-(ω-carboxy-*n*-octyl)benziminazole. This was dissolved in sodium hydroxide solution and the crude dicarboxylic acid precipitated by acetic acid. It was filtered off, recrystallised twice from aqueous acetic acid, and dried for 16 hr. at 80° *in vacuo*. The dicarboxylic acid (36 g.) had m. p. 223—225° (Found: C, 63·8; H, 7·0; N, 8·8%; amine equiv., 325. $C_{17}H_{22}O_4N_2$ requires C, 64·1; H, 6·9; N, 8·8%; amine equiv., 318).

2-(ω-*Methoxycarbonyl*-n-*butyl*)*benziminazole* (II; $R = H$, $R' = CO_2Me$, $x = 4$).—*o*-Phenylenediamine (16·2 g.) and adipic acid (87·6 g.) were boiled under reflux in 4N-hydrochloric acid (200 c.c.) for 21 hr. The solid which was deposited from the cooled solution was filtered off and esterified under reflux for 8 hr. with 3% methanolic hydrogen chloride (200 c.c.). The solution was evaporated to small bulk, then water (500 c.c.) was added. Dimethyl adipate separated as an oil which was removed by repeated extraction with ether. The aqueous solution was neutralised with sodium carbonate, and the *benziminazole* was precipitated, filtered off, and recrystallised from water as white needles (16·1 g.), m. p. 141° (Found: N, 12·2%; amine equiv., 229. $C_{13}H_{16}O_2N_2$ requires N, 12·1%; amine equiv., 232).

2-(ω-*Carboxy*-n-*octyl*)*benziminazole* (II; $R = H$, $R' = CO_2H$, $x = 8$).—*o*-Phenylenediamine (10·8 g.) and sebacic acid (40·4 g.) were heated under reflux in 4N-hydrochloric acid for 4 hr., then cooled and the precipitate was filtered off, washed with water, and dried. Excess of sebacic acid was removed by continuous extraction with ether and the residue crystallised from water. 2-(ω-*Carboxy*-n-*octyl*)*benziminazole hydrochloride* was obtained as white needles (8·5 g.), m. p. 168—170° (Found: Cl, 11·3. $C_{16}H_{23}O_2N_2Cl$ requires Cl, 11·4%). A solution of the hydrochloride (3·1 g.) in warm water (300 ml.) was carefully neutralised with sodium hydroxide solution. The *benziminazolecarboxylic acid* was filtered off and crystallised twice from aqueous ethanol as white needles (2·4 g.), m. p. 117—118° (Found: N, 10·1%; acid equiv., 272; amine equiv., 276·5. $C_{16}H_{22}O_2N_2$ requires N, 10·2%; acid equiv., 274; amine equiv., 274).

4-*Acetamido*-3-*nitrobenzoic Acid*.—4-Acetamido-3-nitrotoluene [7] (400 g.) and magnesium sulphate (400 g.) in water (750 c.c.) were heated to the b. p. An aqueous solution of potassium permanganate (1 kg.) was added during 4 hr. The manganese dioxide was filtered off and the filtrate and washings were concentrated and cooled, unchanged 4-acetamido-3-nitrotoluene (35 g.) being recovered. Acidification of the concentrated solution with hydrochloric acid gave 4-acetamido-3-nitrobenzoic acid (276 g., 67%), m. p. 285—286°.

4-*Amino*-3-*nitrobenzoic Acid*.—4-Acetamido-3-nitrobenzoic acid was boiled under reflux with 5% hydrochloric acid for 1 hr. The solution was cooled and an almost quantitative yield of product, m. p. 284—288°, was filtered off.

This acid with methanol and sulphuric acid gave the methyl ester (95%), m. p. 196—198°.

Methyl 3 : 4-*Diaminobenzoate*.—Methyl 4-amino-3-nitrobenzoate (20 g.) was hydrogenated in ethyl acetate (250 c.c.) and 10% platinum–charcoal (1 g.) at atmospheric pressure until the theoretical quantity of hydrogen had been absorbed. The catalyst was removed; the filtrate was dried ($CaCl_2$) and evaporated. The yield of product, m. p. 108—109°, was quantitative.

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