59. *Some* N-*Substituted* 2-*Oxobenzimidazolines.*

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N-Substituted 2-oxobenzimidazolines are accessible by alkylation of 1-isopropenyl-2-oxobenzimidazoline followed by acid hydrolysis, and from *N*-alkyl-2-nitroanilines.

The preparation of 1-methyl-2-oxobenzimidazoline from the readily available 1-isopropenyl-2-oxobenzimidazoline by alkylation followed by acid hydrolysis [1] has been extended to a series of 1-substituted 2-oxobenzimidazolines. These are listed, together with some derived compounds, in Table 1. 3-Acetyl- and 3-diethylcarbamoyl-1-isopropenyl-2-oxobenzimidazoline were also prepared, but could not be hydrolysed to 1-acyl-2-oxobenzimidazolines.

N-Substituted 2-oxobenzimidazolines with substituents in the benzene ring were prepared from appropriate *N*-alkyl-*o*-nitroanilines by treatment with alkyl chloroformates followed by reduction to *N*-alkoxycarbonyl-*N*-alkyl-*o*-phenylenediamines, which were then cyclised by sodium alkoxides to the required compounds. Alternatively, the nitroanalines were reduced to *N*-alkyl-*o*-phenylenediamines, which were cyclised with urea in boiling 2-butoxyethanol or with ethyl carbonate in the presence of sodium methoxide. 6-Chloro-1-3′-hydroxypropyl-2-oxobenzimidazoline was converted, *via* the 3′-bromopropyl derivative, into 6-chloro-1-3′-dimethylaminopropyl-2-oxobenzimidazoline, an analogue of chlorpromazine. The properties of the 2-oxobenzimidazolines are given in Table 2.

Pharmocological properties of these compounds will be reported elsewhere, but, in brief, the simple 1-alkyl-2-oxobenzimidazolines showed activity as spinal reflex depressants, the duration of action being increased by halogen-substitution in the benzene ring. 6-Chloro-1-ethyl-2-oxobenzimidazoline is now under clinical trial. The chlorpromazine analogue (compound 30) showed virtually no anti-excitant activity.

Experimental

1-*Substituted* 2-*oxobenzimidazolines.*

1-*Alkyl*-2-*oxobenzimidazolines.*—*Standard procedure.* To a solution of sodium ethoxide prepared from sodium (2·3 g.) and absolute ethanol (80 c.c.) was added 1-isopropenyl-2-oxobenzimidazoline (17·4 g.) followed by the halide (1·1—1·4 mol. of chloride for compounds 6 and 11, of bromide for 4, 5, and 9, and of iodide for 1 and 3, and 0·5 mol. of iodide for 7). The halide was added cautiously in cases 5 and 9. The mixture was boiled under reflux for 2—4 hr.

[1] Davoll, preceding paper.

TABLE 1. 1-*Substituted* 2-*oxobenzimidazolines.*

No.	1-Subst.	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N	Form	Solvent [a]	Yield (%)
1	Et	118—120° [c]	66·6	6·2	16·8	$C_9H_{10}ON_2$	66·7	6·2	17·3	Prisms	EtOAc	83
2	Pr^n	104	68·1	6·9	15·7	$C_{10}H_{12}ON_2$	68·2	6·9	15·9	Needles	C_6H_6–Pet. [b]	74
3	Bu^n	96	69·5	7·3	14·8	$C_{11}H_{14}ON_2$	69·4	7·4	14·7	Needles	Pet. [c]	82
4	Bu^i	124—126	68·8	7·5	14·8	$C_{11}H_{14}ON_2$	69·4	7·4	14·7	,,	C_6H_6–Pet. [b]	14
5	$CH_2{\cdot}CH{:}CH_2$	95—96	69·4	5·8	16·1	$C_{10}H_{10}ON_2$	69·0	5·8	16·1	,,	EtOAc	75
6	CH_2Ph	197—200	75·1	5·5	12·7	$C_{14}H_{12}ON_2$	75·0	5·4	12·5	,,	EtOH	82
7	1,1′-$[CH_2]_3$ [g]	243—244	65·9	5·6	18·3	$C_{17}H_{16}O_2N_4$	66·2	5·2	18·2	,,	EtOH	38
8	$CH_2{\cdot}CH_2{\cdot}NEt_2$	48—55 [d]	67·2	8·4	18·3	$C_{13}H_{19}ON_3$	66·9	8·2	18·0	—	—	64
9	$CH_2{\cdot}CO_2Et$	175—176	59·8	5·5	12·8	$C_{11}H_{12}O_3N_2$	60·0	5·5	12·7	Needles	EtOH	69
10	$CH_2{\cdot}CO_2H$	237—240 [e]	56·5	4·4	14·7	$C_9H_8O_3N_2$	56·3	4·2	14·6	Prisms	EtOH	62
11	$CH_2{\cdot}CO{\cdot}NEt_2$	130—132	63·3	7·2	17·1	$C_{13}H_{17}O_2N_3$	63·1	6·9	17·0	,,	EtOAc	77
12	$CH_2{\cdot}OH$	155—157	58·4	5·0	17·1	$C_8H_8O_2N_2$	58·5	4·9	17·1	Needles	H_2O	61
13	$CH_2{\cdot}CH_2{\cdot}OH$	140—141	60·9	5·6	15·8	$C_9H_{10}O_2N_2$	60·7	5·7	15·7	Blades	H_2O	75
14	$CH_2{\cdot}CH_2Cl$	150—151	54·6	4·6	14·1 [f]	$C_9H_9ON_2Cl$	55·0	4·6	14·3	Needles	EtOH	44
15	$CH_2{\cdot}CH(OH){\cdot}CH_2{\cdot}OH$	140—143	58·0	5·7	13·8	$C_{10}H_{12}O_3N_2$	57·7	5·8	13·5	,,	H_2O	80

[a] Pet. = light petroleum. [b] B. p. 40—60°. [c] B. p. 80—100°. [d] B. p. 184°/0·3 mm. [e] Decomp.
[f] Found: Cl, 18·1. Req. Cl, 18·0%. [g] *i.e.* 1,1′-Trimethylenedi-(2-oxobenzimidazoline).

TABLE 2. 1-*Substituted* Bz-*substituted* 2-*oxobenzimidazolines.*

No.	1-Subst.	*Bz*-Subst.	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N	Solvent	Route	Yield (%)
16	Et	5-Cl	168—170°	55·0	4·9	14·4	$C_9H_9ON_2Cl$	55·0	4·6	14·3	EtOH–H_2O	C	54
17	Et	6-Cl	185—186	55·0	4·5	14·5	$C_9H_9ON_2Cl$	55·0	4·6	14·3	EtOAc	D	85
18	Et	7-Cl	170	55·0	4·7	14·3	$C_9H_9ON_2Cl$	55·0	4·6	14·3	EtOH–H_2O	A	49
19	Et	5,6-Cl_2	207—208	46·9	3·5	12·0	$C_9H_8ON_2Cl_2$	46·8	3·5	12·1	EtOAc	C	49
20	Et	5-CO_2H	317—320	58·4	4·8	13·9	$C_{10}H_{10}O_3N_2$	58·2	4·9	13·6	EtOH	C	29
21	Et	5-NH·COMe	246—248	60·2	6·2	19·2	$C_{11}H_{13}O_2N_3$	60·3	6·0	19·2	EtOH	—	83
22	Et	5-Me	118	68·7	7·0	16·2	$C_{10}H_{12}ON_2$	68·2	6·9	15·9	C_6H_6–Pet. [b]	C	41
23	Et	5-OMe	145	62·9	6·2	15·0	$C_{10}H_{12}O_2N_2$	62·5	6·3	14·6	EtOAc	C	10
24	Et	5-OEt	119—120	64·1	7·2	13·8	$C_{11}H_{14}O_2N_2$	64·1	6·8	13·6	EtOAc	C	40
25	Et	5,5′-CH_2 [c]	350—351	67·1	5·8	17·0	$C_{19}H_{20}O_2N_4$	67·8	6·0	16·7	AcOH–H_2O	C	68
26	$CH_2{\cdot}CH{=}CH_2$	6-Cl	173—175	57·7	4·4	13·4	$C_{10}H_9ON_2Cl$	57·6	4·4	13·4	EtOAc	B	50
27	$CH_2{\cdot}CH{=}CH_2$	5,6-Cl_2	196—198	49·3	3·4	11·6	$C_{10}H_8ON_2Cl_2$	49·4	3·3	11·5	EtOAc	B	70
28	$(CH_2)_3{\cdot}OH$	6-Cl	166—168	53·3	4·8	12·2	$C_{10}H_{11}O_2N_2Cl$	53·0	5·0	12·4	EtOAc	C	74
29	$(CH_2)_3Br$	6-Cl	133—134	41·7	3·2	9·5	$C_{10}H_{10}ON_2ClBr$	41·5	3·5	9·7	EtOAc	—	65
30	$(CH_2)_3{\cdot}NMe_2$	6-Cl	118—119	57·0	6·6	16·7	$C_{12}H_{16}ON_3Cl$	56·8	6·4	16·6	EtOAc	—	78

[a] Based on last crystalline intermediate. [b] Pet. = light petroleum (b. p. 40—60°). [c] *i.e.* 5,5′-Methylenedi-(1-ethyl-2-oxobenzimidazoline).

(20 hr. for compound 4), cooled, and treated with 20N-sulphuric acid (10 c.c.). After 2 hr. at 20° an equal volume of water was added and the mixture was evaporated to about half-bulk. The crude *product*, usually contaminated with a little 2-oxobenzimidazoline, was collected and recrystallised (see Table 1).

1-2′-*Diethylaminoethyl*-2-*oxobenzimidazoline*.—To a solution of sodium ethoxide prepared from sodium (1·38 g., 2 atom-equiv.) and absolute ethanol (60 c.c.) were added successively 1-isopropenyl-2-oxobenzimidazoline (5·22 g., 1 mol.) and a solution of 2-diethylaminoethyl chloride hydrochloride (5·16 g., 1 mol.) in hot absolute ethanol (20 c.c.). The mixture was boiled under reflux for 6 hr., cooled, and filtered, and the filtrate was treated with 20N-sulphuric acid (4 c.c.). After 2 hr. at 20°, the mixture was evaporated, the residue treated with excess of aqueous potassium carbonate, and the product isolated with chloroform and distilled.

1-*Hydroxymethyl*-2-*oxobenzimidazoline*.—1-Isopropenyl-2-oxobenzimidazoline (20·9 g.), 40% aqueous formaldehyde (30 c.c.), and water (180 c.c.) were boiled together under reflux for 45 min. A little ethanol was added to give a clear solution, which was refluxed for a further 15 min. and cooled. 1-Hydroxymethyl-3-isopropenyl-2-oxobenzimidazoline (20·5 g., 84%) separated as a lower liquid layer which crystallised on washing with water and had m. p. 78—86°. A solution of this (20·5 g.) in hot ethanol (60 c.c.) was cooled rapidly, treated with 10N-hydrochloric acid (4 c.c.), and, after 2 hr. at 20°, evaporated below 40° to half-volume, diluted with water, and evaporated again. The product (9·5 g.) was pure after being washed with ethanol, but could be recrystallised rapidly from water.

1-2′-*Hydroxyethyl*-2-*oxobenzimidazoline*.—To a solution of 1-isopropenyl-2-oxobenzimidazoline (5·22 g., 1 mol.) in cold absolute ethanol (60 c.c.) containing sodium ethoxide (50 mg.) was added ethylene oxide (3·71 c.c., 2·5 mol.). After 18 hr. at 20° the mixture was boiled under reflux for 2 hr., one-third of the ethanol distilled off, and concentrated hydrochloric acid (3 c.c.) added. After 2 hr. at 20°, the mixture was evaporated to dryness and the residue crystallised from water (yield, 4·0 g.).

1-(2,3-*Dihydroxypropyl*)-2-*oxobenzimidazoline*.—A mixture of 1-isopropenyl-2-oxobenzimidazoline (20·9 g., 1 mol.) and glycide (9·8 g., 1·1 mol.) was heated cautiously to 115—120° (internal temperature), the temperature rising spontaneously to 225°. After cooling, the product was hydrolysed as in the previous example.

1-*Propyl*-2-*oxobenzimidazoline*.—This was prepared by hydrogenation of the 1-allyl derivative in ethanol, with palladium oxide as catalyst.

2-*Oxobenzimidazolin*-1-*ylacetic Acid*.—This separated when a solution of the ethyl ester (10·4 g.) in 2N-sodium hydroxide (71 c.c.) was kept for 3 days at 20° and then acidified with concentrated hydrochloric acid.

1-2′-*Chloroethyl*-2-*oxobenzimidazoline*.—To a solution of the hydroxyethyl compound (1·8 g.) in dry benzene (4 c.c.) and pyridine (0·8 c.c.) was added thionyl chloride (1 c.c.). After 3 hr. benzene and 0·5N-hydrochloric acid were added, and the chloroethyl compound (0·86 g.) was isolated by evaporation of the dried (Na_2SO_4) organic layer.

3-*Acetyl*-1-*isopropenyl*-2-*oxobenzimidazoline*.—Acetylation of the isopropenyl compound with acetic anhydride–pyridine at the b. p. and addition to water gave the *acetyl derivative* (97%) as needles (from 50% ethanol), m. p. 109° (Found: C, 66·3; H, 5·9; N, 13·1. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·6; N, 13·0%). The compound was unaffected by ethanolic 2N-sulphuric acid at 20°, and was hydrolysed to 2-oxobenzimidazoline at the b. p.

3-*Acetyl*-1-*ethyl*-2-*oxobenzimidazoline*.—Prepared by using boiling acetic anhydride, the *acetyl derivative* (91%) formed needles (from ethanol), m. p. 110—112° (Found: C, 65·1; H, 6·2; N, 13·9. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9; N, 13·7%).

1-*Ethyl*-3-*hydroxymethyl*-2-*oxobenzimidazoline*.—1-Ethyl-2-oxobenzimidazoline (6·48 g.), 40% aqueous formaldehyde (10 c.c.), and water (60 c.c.) were boiled under reflux for 1 hr. The *hydroxymethyl compound* (6·74 g., 88%) separated on cooling; it formed plates (on rapid crystallisation from water), m. p. 132—135° (Found: 62·6; H, 6·3; N, 14·8. $C_{10}H_{12}O_2N_2$ requires C, 62·5; H, 6·3; N, 14·6%).

3-*Diethylcarbamoyl*-1-*ethyl*-2-*oxobenzimidazoline*.—To a solution of sodium ethoxide prepared from sodium (0·92 g., 1 mol.) and absolute ethanol (40 c.c.) was added 1-ethyl-2-oxobenzimidazoline (6·48 g., 1 mol.) followed by benzene (300 c.c.). Ethanol was removed by azeotropic distillation through a short column (170 c.c. of distillate), and the residual pasty mass was treated with diethylcarbamoyl chloride (5·96 g., 1·1 mol.). The mixture was boiled under reflux with stirring for 4 hr., then cooled, and the clear solution was washed with water and dried

(Na_2SO_4). Evaporation and distillation gave the *diethylcarbamoyl compound* (8·62 g., 83%), b. p. 158—162°/0·4 mm. (Found: C, 64·5; H, 7·5; N, 16·7. $C_{14}H_{19}O_2N_3$ requires C, 64·3; H, 7·3; N, 16·1%).

Similarly, 1-isopropenyl-2-oxobenzimidazoline gave 3-*diethylcarbamoyl*-1-*isopropenyl*-2-*oxobenzimidazoline*, b. p. 156—164°/0·2—0·3 mm. (Found: C, 65·7; H, 6·9; N, 16·1. $C_{15}H_{19}O_2N_3$ requires C, 65·9; H, 7·0; N, 15·4%), which was unaffected by 2N-sulphuric acid in aqueous ethanol at room temperature.

Bz-*Substituted* 1-*alkyl*-2-*oxobenzimidazolines*.

N-*Alkyl*-o-*nitroanilines*.—With the exception of 4,4′-methylenedi-(*N*-ethyl-*o*-nitroaniline), these were prepared as follows. 1,4-Dichloro-2-nitrobenzene, 1,2-dichloro-3-nitrobenzene, 4-bromo-3-nitroanisole, 4-bromo-3-nitrophenetole, 4-bromo-3-nitrotoluene, and 4-bromo-3-nitrobenzoic acid were heated with ethanolic ethylamine (2 mol.) at 150° for 15 hr., non-crystalline products being isolated with ether and used directly. 2,4-Dichloro-1-nitrobenzene in 2-ethoxyethanol (5 vol.) was heated under reflux on the steam-bath for 12 hr. with 4 mol. of 70% aqueous ethylamine or boiled under reflux for 5 hr. with 2 mol. of allylamine or 3-aminopropanol. In the first case the product separated on cooling, and in the others was isolated with chloroform after evaporation and addition of water. 1,2,4-Trichloro-5-nitrobenzene [2] and the amine (2 mol.) were boiled under reflux for 7 hr. in ethanol.

4,4′-*Methylenedi*-(N-*ethyl*-o-*nitroaniline*).—A mixture of crude *N*-ethyl-*o*-nitroaniline (17·5 g.), concentrated hydrochloric acid (13 c.c.), and 30% aqueous formaldehyde (3·8 c.c.) was kept overnight, then boiled for 5 hr. under reflux. Collected after cooling, the methylene derivative (14·4 g., 79%) formed needles (from ethanol), m. p. 120—122° (Found: C, 59·7; H, 6·1; N, 16·3. $C_{17}H_{20}O_4N_4$ requires C, 59·3; H, 5·9; N, 16·3%).

N-*Alkyl*-o-*phenylenediamines*.—2-Amino-6-chloro-*N*-methylaniline was prepared by catalytic hydrogenation in ethanol with platinum oxide. For the other compounds, the following procedure was typical. A mixture of *N*-alkyl-5-chloro-2-nitroaniline (174 g.), iron powder (110 g.), water (170 c.c.), and ethanol (170 c.c.) was stirred on the steam-bath under reflux while a mixture of concentrated hydrochloric acid (8·3 c.c.), water (37 c.c.), and ethanol (37 c.c.) was cautiously added. The mixture was then boiled under reflux with stirring for 45 min., basified with sodium hydrogen carbonate solution, and filtered, and the solid was washed with ethanol. The filtrate was diluted with water, and the product isolated with chloroform; it was sufficiently pure for further use. Distillation gave 80—90% of pure product, but distillation of large quantities of the halogeno-derivatives occasionally led to explosive decomposition. Prepared in this way were 2-*amino*-5-*chloro*-N-*ethyl*-, b. p. 122—123°/1 mm., N-*allyl*-2-*amino*-5-*chloro*-, b. p. 135—136°/1·5 mm., N-*allyl*-2-*amino*-4,5-*dichloro*-, b. p. 145°/0·3 mm. (Found: C, 49·6; H, 4·5. $C_9H_{10}N_2Cl_2$ requires C, 49·6; H, 4·5%), and 2-*amino*-4,5-*dichloro*-N-*ethylaniline*, b. p. 138—140°/0·2 mm., m. p. 43—45° (Found: C, 47·6; H, 5·0. $C_8H_{10}N_2Cl_2$ requires C, 46·8; H, 4·9%). All darkened rapidly in air.

Bz-*Substituted* 1-*Alkyl*-2-*oxobenzimidazolines*.—(*A*) The crude diamine and urea (3 mol.) were heated for 1 hr. at 180—190°. After cooling, the product was dissolved in sodium hydroxide solution, treated with charcoal, and precipitated with acid.

(*B*) The crude diamine, urea (2 mol.), and 2-butoxyethanol (4 c.c./g. of diamine) were boiled under reflux for 3 hr. and added to water (5 volumes), and the crude product was washed with light petroleum (b. p. 40—60°).

(*C*) The *N*-alkyl-*o*-nitroaniline was boiled under reflux for 3 hr. with an excess of ethyl chloroformate (compounds 16, 20, 22—25) or butyl chloroformate (compounds 19, 28). The cooled mixture was treated with ethanol, kept overnight, and evaporated to a syrup, which was hydrogenated in ethanol with platinum oxide. After removal of catalyst and solvent, the residue was boiled under reflux for 2 hr. with a solution prepared from sodium (1 atom-equiv.) and ethanol (compounds 16, 22, 23) or 2-ethoxyethanol (compounds 19, 20, 24, 25, 28). The cooled solution was concentrated, diluted with water, and acidified.

In the preparation of compound 20, 4-ethylamino-3-nitrobenzoic acid was first converted into the ethyl ester. After cyclisation to the 2-oxobenzimidazoline the mixture was refluxed with excess of sodium hydroxide to hydrolyse the ester group.

(*D*) The crude diamine, toluene (4 c.c./g.), ethyl carbonate (1·25 mol.), and sodium methoxide (1·1 mol.) were stirred together under a column while the temperature was raised

[2] B.I.O.S. Final Report, No. 986, Item 2, Part II; Process No. 194.

cautiously to 100°. When the distillation of azeotropes slackened the bath temperature was raised during 5 hr., finally to 170°. After cooling, water and acetic acid were added and the product was collected and washed with light petroleum (b. p. 40—60°).

5-Acetamido-1-ethyl-2-oxobenzimidazoline.—1-Ethyl-5-nitro-2-oxobenzimidazoline [3] (1 g.), suspended in glacial acetic acid (20 c.c.), was hydrogenated, with platinum oxide as catalyst. After removal of catalyst and solvent the residue was dissolved in water (15 c.c.) and treated with acetic anhydride (5 c.c.). After 1 hr., the acetamido-compound was isolated by partial evaporation and addition of water.

6-Chloro-1-3′-dimethylaminopropyl-2-oxobenzimidazoline.—Crude 5-chloro-*N*-3′-hydroxypropyl-2-nitroaniline (22·6 g.) in dry benzene (60 c.c.) and pyridine (8 c.c.) was treated with benzoyl chloride (11·6 c.c.). After 2 hr. the mixture was filtered and the filtrate washed with dilute hydrochloric acid and aqueous sodium carbonate. Evaporation gave N-3′-*benzoyloxypropyl-5-chloro-2-nitroaniline* (23·5 g., 72%) as orange needles, m. p. 105° (Found: C, 57·3; H, 4·6; N, 8·7. $C_{16}H_{15}O_4N_2Cl$ requires C, 57·4; H, 4·5; N, 8·4%). Conversion of this compound into a 2-oxobenzimidazoline by method C (with 2 mol. of sodium 2-ethoxyethoxide) simultaneously removed the benzoyl group, giving 6-chloro-1-3′-hydroxypropyl-2-oxobenzimidazoline. This (2 g.) and 48% hydrobromic acid (10 c.c.) were boiled under reflux for 1 hr. After cooling, the 3′-bromopropyl compound (2·3 g., 90%) was isolated with chloroform. The bromo-compound (14·4 g.) and ethanolic dimethylamine (90 c.c. of 33%) were boiled together under reflux for 4 hr. The mixture was evaporated and treated with aqueous potassium carbonate, and the 3′-dimethylaminopropyl compound isolated with chloroform.

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