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The Synthesis of 1-Substituted-2-(β-dimethylaminoethyl)benzimidazoles

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2-(β-Dimethylaminoethyl)benzimidazoles have been prepared by the reduction of the corresponding 2-benzimidazole-*N*,*N*-dimethylacetamides. Condensation of ethyl cyanoacetate with *N*-benzyl or phenyl-*o*-phenylenediamines led to *N*-cyanoacetyl-*N*'-substituted-*o*-phenylenediamines, the structure of which were assigned from u.v. and n.m.r. data. An improved synthesis of benzimidazole-2-acetic acid derivatives, from substituted ethyl acetimidates and *o*-phenylenediamines, is described. Dimerisation of 1-phenylbenzimidazole occurs in the presence of phenyllithium.

The biological properties of 2-dialkylaminomethylbenzimidazoles have been reported by several investigators (2-4), but 2-(β-dialkylaminoethyl)benzimidazoles have not been described. We required these compounds (V; R = H, $CH_2C_6H_5$ or C_6H_5) for pharmacological testing, and this paper describes a number of synthetic routes which were investigated. One of these appears to be general for the synthesis of 1-substituted-2-(β-dialkylaminoethyl)-benzimidazoles.

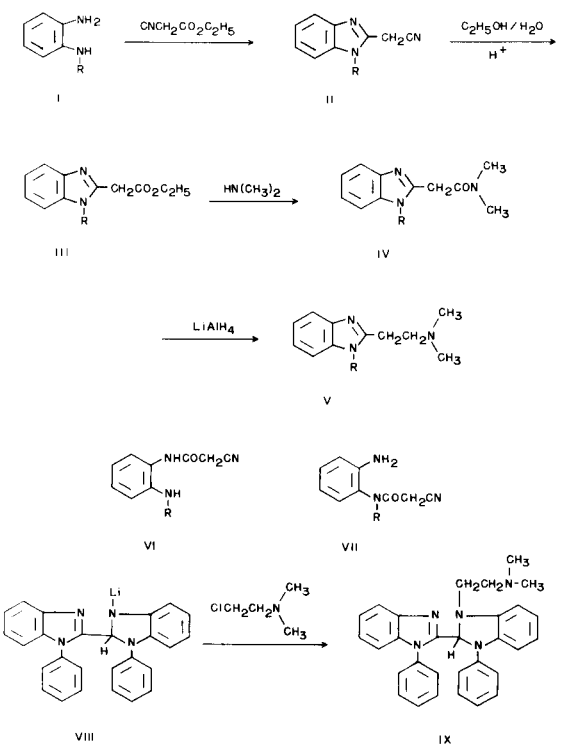
Roeder and Day (4) obtained 2-(α-dialkylaminoethyl)benzimidazoles by the action of amines on 2-(α-chloroethyl)benzimidazole. A similar reaction with 2-(β-chloroethyl)benzimidazole and dimethylamine produced intractable tars, probably as a consequence of the instability of this compound (5) and we were unable to isolate the required amine (V; R = H).

A synthesis of the amine (V; R = H) was effected by the series of transformations shown in Scheme 1. *o*-Phenylenediamine (I; R = H) was converted, via the nitrile (II; R = H), into the ester (III; R = H), according to the method of Copeland and Day (6). Reaction of the ester with ethanolic dimethylamine afforded the amide (IV; R = H) which, after reduction with lithium aluminum hydride, gave the required amine (V; R = H).

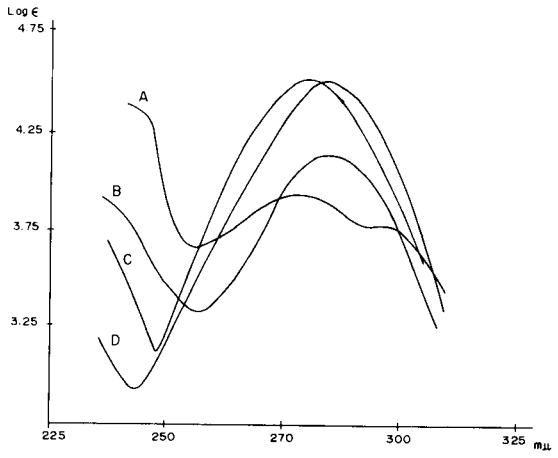
Difficulties were encountered when the substituted *o*-phenylenediamines (I; R = $CH_2C_6H_5$ or C_6H_5) were used due to the stability of the intermediate cyanoacetyl compounds (VI) which were formed from the reaction with ethyl cyanoacetate. *N*-Phenyl-*o*-phenylenediamine gave a mixture of the required benzimidazole (II; R = C_6H_5) and the cyanoacetyl compound (VI; R = $CH_2C_6H_5$), whereas *N*-benzyl-*o*-phenylenediamine gave only the non cyclic product (VI; R = C_6H_5). Neither of the cyanoacetyl compounds (VI) could be cyclised by boiling in nitrobenzene (3) or acetic anhydride (7), but low yields of the benzimidazoles (II; R = $CH_2C_6H_5$ or C_6H_5) were obtained by heating in boiling ethyl cyanoacetate or above the melting point *in vacuo*. Boiling 4 *N* hydrochloric acid was examined as a medium (4) for cyclization of the benzyl compound (VI; R = $CH_2C_6H_5$), but was unsatisfactory since, although cyclisation occurred, hydrolysis of the nitrile group and decarboxylation led to the formation of 1-benzyl-2-methylbenzimidazole.

The cyanoacetyl compounds (VI), in their reluctance towards cyclisation, resemble *N*-methyl-*N*-acetyl-*o*-phenylenediamine. Roeder and Day postulated (4) that the tertiary amidic structure of the latter compound prevented cyclization to 1,2-dimethylbenzimidazole, and this prompted us to confirm the structure (VI) over the alternative (VII) for the cyanoacetyl compounds.

The absence of a primary anilino function (structure VII) in the cyanoacetyl compounds was indicated by their failure to form benzylidene derivatives with benzaldehyde. Structure (VI) was confirmed for the phenyl compound (R = C_6H_5) by its ultraviolet absorption and lack of basicity. The spectrum of the phenyl compound in ethanol is unchanged by the addition of hydrochloric acid (Fig. 1, curve B). This spectrum is similar to the absorption of *N*-phenyl-*o*-phenylenediamine hydrochloride (Fig. 1, curve C) and diphenylamine (Fig. 1, curve D) rather than *N*-phenyl-*o*-phenylenediamine base (Fig. 1, curve A) where the lone-pair of electrons (in the primary amino group) are still available for n-π* transitions. In the benzyl compound (R = $CH_2C_6H_5$) the ultraviolet data were equivocal and the structure (VI) was confirmed from the n.m.r. spectrum. This was recorded on a Varian H-100 in hexadeuterodimethylsulfoxide using tetramethylsilane as an external reference (8). The spectrum showed two distinct and widely separated signals at τ = 0.5 (singlet) and τ = 4.18 (broad triplet), attributable to amidic and amino -NH respectively, in addition to the other protons at τ = 2.3 - 3.7 (aromatic multiplet), 5.56 (benzylic doublet) and 6.01 (methylenic singlet). Irradiation at 4.18 τ reduced the doublet at 5.56 τ to a singlet, thus demonstrating the coupling between the benzylic and amino protons



and confirming the assignments. This certainly eliminates structure (VII) where such coupling is not possible. The n.m.r. spectrum of the phenyl compound also supported the structural assignment (VI; R = C_6H_5) showing singlets at τ = 0.5 and 6.1,



(A) *N*-Phenyl-*o*-phenylenediamine. (B) *N*-Cyanoacetyl-*N*'-phenyl-*o*-phenylenediamine. (C) *N*-Phenyl-*o*-phenylenediamine hydrochloride. (D) Diphenylamine.

Fig. I. Ultraviolet Spectra of Diphenylamine Derivatives in Ethanol.

attributable to amidic and methylenic protons respectively. The amino proton was not distinguishable and a similar effect was observed for diphenylamine in this solvent.

The difficulties encountered in obtaining the substituted nitriles (II) prompted us to investigate other routes to the esters (III), and we found that the reaction of ethyl carboethoxyacetimidate with the *o*-phenylenediamines (I) provided a satisfactory procedure (9). The substituted esters (III; R = $CH_2C_6H_5$ or C_6H_5) could not, however, be converted into the corresponding dimethylamides (IV; R = $CH_2C_6H_5$ or C_6H_5) even after prolonged exposure to dimethylamine at 100°. An alternative route via hydrolysis to the corresponding 1-substituted-benzimidazole-2-acetic acids was prevented by their spontaneous decarboxylation. The amides (IV) were, however, obtained in excellent yields from the *o*-phenylenediamines (I) and ethyl *N*,*N*-dimethylcarboxamidoacetimidate. Reduction of the amides (IV) was effected by lithium aluminum hydride, and the amines (V; R = H or $CH_2C_6H_5$) were obtained without difficulty. When the substituent (R) was phenyl, however, isolation of the amine was complicated by the presence of other products and the formation of at least seven nitrogenous compounds was demonstrated by using a thin layer chromatographic technique.

An attempt to obtain the amines (V) directly from the *o*-phenylenediamines (I) by reaction with ethyl 2-(dimethylamino)propionimidate was forestalled by our inability to isolate this imino-ether from 2-(dimethylamino)propionitrile by procedures which have been effective for other aminoalkyl nitriles (10).

Since none of the foregoing procedures was entirely satisfactory for the preparation of the amine (V; R = C_6H_5), a synthesis from 1-phenyl-2-benzimidazolyllithium and β-dimethylaminoethyl chloride was investigated (11). The reaction afforded a high melting orange solid, which is tentatively assigned structure (IX) on the basis of its ultraviolet absorption, which resembles a 1-phenylbenzimidazole, infrared spectrum (no evidence of other functional groups or of N-H), molecular weight, mass spectrum and elemental analysis. Product (IX) probably arose via coupling of 1-phenyl-2-benzimidazolyllithium with 1-phenylbenzimidazole and subsequent alkylation of the resulting lithio derivative (VIII). A similar dimerisation of 1-methylbenzimidazole, in the presence of *n*-butyllithium, has been reported by Alley and Shirley (12).

EXPERIMENTAL

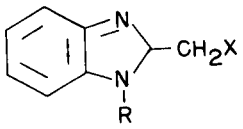
o-Phenylenediamine (B.D.H.) and *N*-phenyl-*o*-phenylenediamine (Koch-Light) were crystallized before use. Ethyl cyanoacetate (B.D.H.) was distilled. Melting points were recorded on an Electrothermal ® apparatus comprising a gas heated block and a thermometer calibrated for stem exposure. Micro-analyses are by Mr. M. J. Graham, Smith Kline and French Laboratories Ltd.

2-Cyanomethyl-1-phenylbenzimidazole (II; R = C_6H_5).

Ethyl cyanoacetate (22.6 g., 0.2 mole) containing *N*-phenyl-*o*-phenylenediamine (19 g., 0.105 mole) was boiled under reflux for 1 hour. After being cooled the mixture was diluted with benzene and

TABLE I

Benzimidazole-2-acetic Acid Derivatives Prepared from Imidates



R	X	Yield, %	M.p., °C	Molecular Formula	Analysis Found, % C	H	N	Calcd., % C	H	N
$-CH_2C_6H_5$	$-CO_2C_2H_5$	88	68-70 (c)	$C_{18}H_{18}N_2O_2$	73.35	6.12	9.6	73.45	6.16	9.5
C_6H_5	$-CO_2C_2H_5$	66 (a)	89-91 (c)	$C_{17}H_{16}N_2O_2$	72.8	5.65	9.9	72.8	5.75	10.0
H	$-CO-N(CH_3)_2$	65 (b)	154-156 (d)	$C_{11}H_{13}N_3O$	65.1	6.79	20.7	65.0	6.45	20.9
$-CH_2C_6H_5$	$-CO-N(CH_3)_2$	56	162-163 (d)	$C_{18}H_{19}N_3O$	73.65	6.34	14.5	73.65	6.53	14.3
C_6H_5	$-CO-N(CH_3)_2$	63	119-121 (e)	$C_{17}H_{17}N_3O$	73.4	6.22	15.2	73.1	6.13	15.0

(a) A similar yield was obtained using the method of Copeland and Day (6). (b) A similar yield was obtained from the ester (X = $CO_2C_2H_5$) and dimethylamine in alcohol at 20° for 48 hours. (c) From petroleum ether b.p. 60-80°. (d) From 2-propanol. (e) From benzene.

the colorless solid was collected and crystallized from ethanol to give *N*-cyanoacetyl-*N'*-phenyl-*o*-phenylenediamine (9 g., 34.5%) as colorless needles with m.p. 163-165°. Infrared ν max (Nujol mull) 1666 (amidic > C=O), 3340 (NH), 2270 (-C≡N) cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.7; H, 5.21; N, 16.7. Found: C, 71.6; H, 5.20; N, 16.5.

The filtrate was shaken with dilute hydrochloric acid and *N*-phenyl-*o*-phenylenediamine hydrochloride, m.p. 205-208°, was precipitated.

The residual mixture of benzene and acid was made alkaline with 40% sodium hydroxide solution, the benzene was separated and the aqueous layer extracted with ether. After being dried (magnesium sulfate), the extracts were evaporated and the residue was crystallised from benzene-petroleum ether (b.p. 60-80°) to give 2-cyanomethyl-1-phenylbenzimidazole (3 g., 12.3%) as colorless prisms, m.p. 121-123°. Ultraviolet λ max (ethanol) mμ (log ϵ) 282.2 (3.46), 274.3 (3.52), 246.3 (3.85).

Anal. Calcd. for $C_{15}H_{11}N_3$: C, 77.2; H, 4.75; N, 18.0. Found: C, 77.5; H, 4.87; N, 18.3.

A similar result was obtained when the reaction time was extended to 16 hours.

N-Benzyl-*N'*-cyanoacetyl-*o*-phenylenediamine (VI; R = $CH_2C_6H_5$).

This compound was obtained in 17.5% yield from *N*-benzyl-*o*-phenylenediamine (20 g., 0.1 mole) and ethyl cyanoacetate (22.6 g., 0.2 mole) using the procedure described above. It crystallised from ethanol as colorless needles with m.p. 160-161°. Infrared ν max (Nujol mull), 1668 (amidic > C=O), 2300 (C≡N), 3400 and 3500 cm^{-1} (NH).

Anal. Calcd. for $C_{16}H_{15}N_3O$: C, 72.4; H, 5.70; N, 15.8. Found: C, 72.5; H, 5.40; N, 16.0.

Cyclisation of *N*-Cyanoacetyl-*N'*-phenyl-*o*-phenylenediamine. Method A.

N-Cyanoacetyl-*N'*-phenyl-*o*-phenylenediamine (9 g., 0.04 mole) was heated *in vacuo* at 180-200° for 1 hour to give 2-cyanomethyl-1-phenylbenzimidazole (3 g., 36%).

Method B.

Ethyl cyanoacetate (10 ml.) containing *N*-cyanoacetyl-*N'*-phenyl-*o*-phenylenediamine (2.5 g., 0.01 mole) was boiled under reflux for 1 hour and then worked up as described above to give 0.9 g., (39%) of 2-cyanomethyl-1-phenylbenzimidazole.

Cyclization of *N*-Benzyl-*N'*-cyanoacetyl-*o*-phenylenediamine. Method A.

N-Benzyl-*N'*-cyanoacetyl-*o*-phenylenediamine (1 g., 0.004 mole) was heated *in vacuo* at 200° for 2 hours and crystallisation of the residue from 2-propanol gave 1-benzyl-2-cyanomethylbenzimidazole (0.2 g., 20%) as pale yellow prisms, m.p. 137-140°.

Anal. Calcd. for $C_{16}H_{13}N_3$: C, 77.7; H, 5.30; N, 17.0. Found: C, 77.7; H, 5.37; N, 16.8.

Method B.

The method as described for the phenyl compound gave 28% of 1-benzyl-2-cyanomethylbenzimidazole and 50 mg. of a substance, which, after crystallisation from DMF-water, had a melting point of 278-280° and is possibly *N*-benzyl-*N,N'*-dicyanoacetyl-*o*-phenylenediamine. Infrared ν max (Nujol mull), 1638, 1655 (amidic > C=O), 2200 (C≡N), 3480 cm^{-1} (NH).

Anal. Calcd. for $C_{19}H_{16}N_4O_2$: N, 16.9. Found: N, 17.2.

Method C.

Four normal hydrochloric acid (10 ml.) containing 1 g. (0.004 mole) of the cyanoacetyl compound was boiled under reflux for 20 minutes. The solution was basified at 0° with 40% sodium hydroxide solution and extracted with chloroform. After being dried (magnesium sulfate) the extracts were evaporated to give 1-benzyl-2-methylbenzimidazole as an oil. The picrate had a melting point of 193-194° from methanol.

Anal. Calcd. for $C_{21}H_{17}N_5O_7$: C, 55.9; H, 3.80; N, 15.5. Found: C, 56.1; H, 3.67; N, 15.8.

Preparation of Benzimidazole-2-acetic Acid Derivatives.

All compounds (Table I) were prepared by the same general method, which is exemplified below in the case of ethyl 2-benzimidazole-acetate.

Absolute ethanol (75 ml.) containing *o*-phenylenediamine (16.2 g., 0.15 mole) and ethyl carboethoxyacetimidate hydrochloride (14) (29.2 g., 0.15 mole) was boiled under reflux for 2 hours. Ammonium chloride was filtered off and the filtrate was evaporated under reduced pressure. The residue was suspended in 200 ml. of water and extracted with chloroform. After being dried (magnesium sulfate) the

extracts were evaporated to give ethyl 2-benzimidazole-acetate (25 g., 82%), m.p. 125-127°, which gave no depression on admixture with a sample prepared according to the method of Copeland and Day (6).

Ethyl 2-*N*,*N*-Dimethylcarboxamido-acetimidate Hydrochloride.

Anhydrous chloroform (100 ml.) containing *N*,*N*-dimethylcyano-acetamide (13) (11.2 g., 0.1 mole) and absolute ethanol (4.6 g., 0.1 mole) was saturated with anhydrous hydrogen chloride at 0°. The resulting colorless crystalline solid was collected, washed with anhydrous ether and then dried *in vacuo* over potassium hydroxide to give ethyl 2-*N*,*N*-dimethylcarboxamido-acetimidate hydrochloride as a colorless hygroscopic solid (10 g., 51.5%), m.p. 124-125°.

Anal. Calcd. for $C_7H_{14}N_2O_2 \cdot HCl$: C, 43.2; H, 7.77; N, 14.4. Found: C, 43.3; H, 7.86; N, 14.5.

2-(β-Dimethylaminoethyl)benzimidazole (V; R = H).

A suspension of 2-benzimidazole-*N*,*N*-dimethylacetamide (2.6 g., 0.013 mole) in 30 ml. of anhydrous ether was slowly added to a stirred suspension of lithium aluminum hydride (1.5 g., 0.037 mole) in 25 ml. of anhydrous ether. The mixture was boiled under reflux for 4 hours, cooled to 0°, and the excess of lithium aluminum hydride was destroyed by the addition of wet ether and then saturated ammonium chloride solution. The mixture was filtered and the ether was separated from the aqueous layer which was then saturated with sodium chloride and again extracted with ether. After being dried (magnesium sulfate) the combined extracts were evaporated and crystallisation of the residue from benzene-petroleum ether (b.p. 60-80°) gave 2-(β-dimethylaminoethyl)benzimidazole as colorless needles (1.8 g., 77%), m.p. 125-127°. Ultraviolet λ max (ethanol), mμ (log ε) 280.6 (3.96), 274.1 (3.90), 243 (3.83).

Anal. Calcd. for $C_{11}H_{15}N_3$: C, 69.8; H, 7.99; N, 22.2. Found: C, 69.9; H, 7.83; N, 22.0.

1-Benzyl-2-(β-dimethylaminoethyl)benzimidazole (V; R = $CH_2C_6H_5$).

This compound was prepared in 36% yield by reduction of 19 g. (0.065 mole) of 1-benzylbenzimidazole-2-*N*,*N*-dimethylacetamide, using the procedure described above. It had a melting point of 72-74° from petroleum ether (60-80°). Ultraviolet λ max (ethanol) mμ (log ε) 292.2 (3.67), 281.7 (3.81), 273 (3.82).

Anal. Calcd. for $C_{18}H_{21}N_3$: C, 77.4; H, 7.58; N, 15.0. Found: C, 77.3; H, 7.39; N, 15.0.

2-(β-Dimethylaminoethyl)-1-phenylbenzimidazole (V; R = C_6H_5).

Reduction of 20 g. (0.072 mole) of 1-phenylbenzimidazole-2-*N*,*N*-dimethylacetamide, using the procedure described above, gave an oily mixture which, with hydrogen chloride in 2-propanol, gave the dihydrochloride of the product (8% yield), m.p. 173-175° from ethanol. Ultraviolet λ max (ethanol), mμ (log ε) 282.2 (3.76), 274.5 (3.79), 246 (4.10).

Anal. Calcd. for $C_{17}H_{19}N_3 \cdot 2HCl$: C, 60.35; H, 6.26; N, 12.4; Cl, 21.0. Found: C, 60.0; H, 6.30; N, 12.1; Cl, 20.5.

2-(β-Dimethylaminoethyl)-1-phenylbenzimidazole.

This compound was obtained by neutralisation of the dihydrochloride, and had a melting point of 63-65° from petroleum ether (b.p. 40-60°). Ultraviolet λ max (ethanol), mμ (log ε) 283 (3.50), 276 (3.52), 267 (3.49), 247.5 (3.79).

Anal. Calcd. for $C_{17}H_{19}N_3$: C, 76.9; H, 7.22; N, 15.8. Found: C, 76.7; H, 7.39; N, 15.7.

1-(β-Dimethylaminoethyl)-3-phenyl-2-(1'-phenylbenzimidazol-2'-yl)-benzimidazoline.

Phenyllithium (0.015 mole) in 55 ml. of anhydrous ether was stirred at 0°, in an atmosphere of nitrogen, and to this a solution of 1-phenylbenzimidazole (3 g., 0.0155 mole) in 30 ml. of dry benzene was added. The mixture was stirred at 20-25° for 2.5 hours, and then a solution of β-dimethylaminoethyl chloride (2.35 g., 0.022 mole) in 30 ml. of dry benzene was added. The mixture was boiled under reflux for 3 hours, cooled to 10°, and then poured onto ice. The organic layer was separated off, and the aqueous layer was extracted with ether. After being dried (magnesium sulfate) the combined organic solutions were evaporated. The resulting residue was boiled with petroleum ether (b.p. 60-80°) and the insoluble 1-phenylbenzimidazole was collected (0.8 g.). On cooling the petroleum ether solution pale orange needles crystallised and these were recrystallised from ethanol to give 1-(β-dimethylaminoethyl)-3-phenyl-2-(1'-phenylbenzimidazol-2'-yl)benzimidazoline as pale orange needles (1 g., 29%), m.p. 191-192°. Ultraviolet λ max (ethanol), mμ (log ε) 286.2 (3.94), 278.4 (3.95), 245.5 (4.22). Infrared (Nujol mull), no absorption between 1610 and 2500 cm^{-1}; (0.8% in carbon tetrachloride) no N-H.

The mass spectrum (15) contained a low intensity parent ion peak at m/e 459 and provided further support for the proposed structure by the presence of two extremely intense fragment peaks at m/e 401 [parent - $CH_2N(CH_3)_2$] and 400 [parent - $CH_2N(CH_3)_2$ - H].

Anal. Calcd. for $C_{30}H_{29}N_5$: C, 78.4; H, 6.36; N, 15.2; mol. wt. 459.6. Found: C, 78.4; H, 6.55; N, 15.05; mol. wt. (Rast) 435.

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