Smith Kline and French Laboratories Ltd.
and
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A New Synthesis of Benzimidazoles and Aza-analogs

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A new procedure for the preparation of benzimidazoles and aza-analogs from *o*-diamines and aldehyde bisulfite adducts is described.

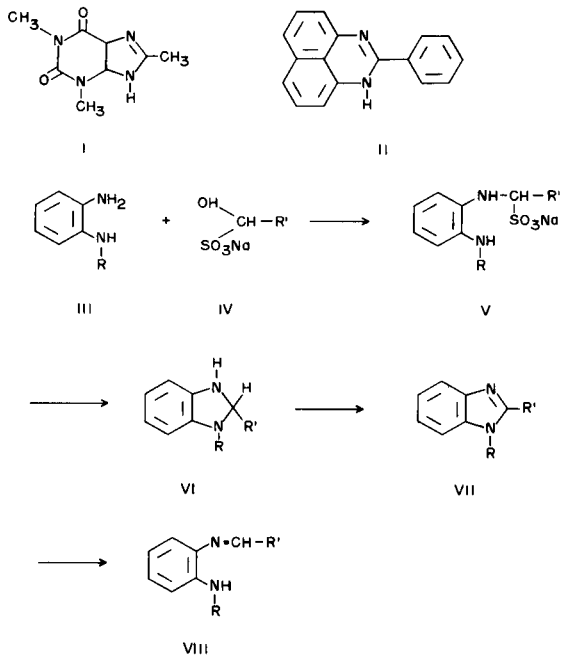
The synthesis of benzimidazoles from *o*-phenylenediamines and aldehydes has hitherto involved the formation and isolation of a Schiffs base followed by oxidative ring closure. Where the Schiffs base has been isolated the oxidising agents used are relatively powerful in their action, for example boiling nitrobenzene (3) or lead tetraacetate (4). Weidenhagen's method (5) in which the Schiffs base is not isolated, involves cupric acetate as the oxidising agent and subsequent decomposition of the copper salt of the benzimidazole is often a tedious procedure. A related method discussed by one of us (6) involved the synthesis of purines by the reaction of a 5-nitroso-4-aminopyrimidine with two equivalents of an aromatic aldehyde, (*cf.* 7).

We now report a simple one step synthesis of benzimidazoles under mild conditions which involves very little risk to labile substituents and which usually gives excellent yields. This consists in reacting an aromatic *o*-diamine (III) with the sodium bisulfite adduct (IV) of an aldehyde in boiling ethanol. In many cases the reaction is complete in a few minutes. It is applicable to both aliphatic and aromatic aldehydes and to a range of substituted *o*-diamines (Tables III and IV). The reaction has also been extended to the synthesis of the purine (I) and the perimidine (II).

We suggest that the reaction proceeds by way of formation of an α-aminosulfonic acid derivative (V), the normal product from the condensation of amines and aldehyde bisulfite adducts (8), followed by intramolecular nucleophilic displacement of sodium sulfite (9) and cyclisation to the benzimidazoline (VI). The rapid dehydrogenation of the latter to the benzimidazole (VII) could then be effected by the bisulfite anion acting as an oxidising agent (*cf.* 10).

An alternate mechanism, whereby the initial condensation product (V) eliminates sodium bisulfite to form a Schiffs base (VIII) (6) which then cyclises, was not supported by experimental evidence. Only a trace of 2-phenylbenzimidazole was obtained after boiling the Schiffs base (VIII) (R' = C_6H_5) in ethanol with one equivalent of sodium bisulfite either in the presence or absence of the bisulfite adduct of benzaldehyde. The Schiffs base (VIII) (R' = C_6H_5) was not detected when the reaction between *o*-phenylenediamine and benzaldehyde bisulfite adduct was followed with thin layer chromatography or ultra-violet spectrophotometry (11).

The reaction between *o*-phenylenediamine and the bisulfite adduct of formaldehyde gave tars from which benzimidazole could not be isolated. The tars probably arose from secondary reactions between benzimidazole and formaldehyde.



EXPERIMENTAL

All melting points were recorded on an electrothermal apparatus with a thermometer calibrated for stem-exposure. Analyses are by Mr. M. Graham (Smith Kline and French Labs. Ltd.).

2-Nitroanilines.

The compounds described in Table I were obtained by the method of Kremer (12).

o-Phenylenediamines.

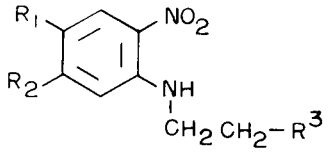
The compounds described in Table II were obtained by reduction of the corresponding nitroaniline with stannous chloride/hydrochloric acid (Method A) or 10% palladium/charcoal - hydrazine (Method B).

Benzimidazoles.

The compounds described in Tables II and IV were prepared by the general method, which is exemplified by the preparation of 2-phenylbenzimidazole.

TABLE I

2-Nitroanilines

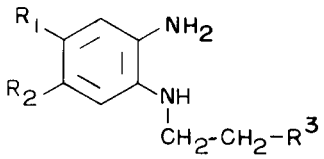


R^1	R^2	R^3	m.p. °C	Literature m.p. °C	Formula	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found	% Nitrogen Calcd.	% Nitrogen Found
H	Cl	$-N(CH_3)_2$	77-78 (c)	80 (a)	$C_{10}H_{14}ClN_3O_2$	-	-	-	-	-	-
H	H	-OH	74-76 (d)	76 (b)	$C_8H_9N_2O_3$	-	-	-	-	-	-
Cl	H	$-N(CH_3)_2$	61-62 (c)	-	$C_{10}H_{14}ClN_3O_2$	49.3	49.4	5.8	5.8	17.2	17.0
CF_3	H	$-N(CH_3)_2$	89-90 (c)	-	$C_{11}H_{14}F_3N_3O_2$	47.7	47.9	5.1	5.3	15.2	15.2
CF_3	H	$-N(CH_2\cdot CH_3)_2$	32-33 (c)	-	$C_{13}H_{18}F_3N_3O_2$	51.1	51.4	6.1	5.9	13.8	13.5

(a) Reference (13). (b) Reference (12). (c) From petroleum-ether. (d) From ethylacetate.

TABLE II

o-Phenylenediamines

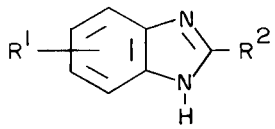


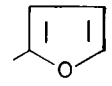
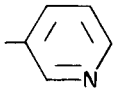
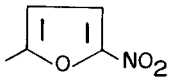
Method	R^1	R^2	R^3	m.p. °C	Literature m.p. °C	Formula	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found	% Nitrogen Calcd.	% Nitrogen Found
A	H	Cl	$-N(CH_3)_2$	217-218 (b)	-	$C_{10}H_{16}ClN_3\cdot 2HCl$	41.9	42.1	6.3	6.6	-	-
B	H	H	-OH	108-110 (c)		$C_8H_{11}N_2O$	-	-	-	-	-	-
A	Cl	H	$-N(CH_3)_2$	207-208 (c)	-	$C_{10}H_{16}ClN_3\cdot 2HCl$	41.9	41.8	6.3	6.3	14.7	14.7
B	CF_3	H	$-N(CH_3)_2$	49-50 (d)	-	$C_{11}H_{16}F_3N_3$	53.4	53.6	6.5	6.5	17.0	16.6
B	CF_3	H	$-N(CH_2\cdot CH_3)_2$	152-153 (c)	-	$C_{13}H_{20}F_3N_3\cdot HCl$	50.1	50.1	6.7	6.4	13.5	13.4

(a) Reference (12). (b) From methanol. (c) From ethanol. (d) From petroleumether.

TABLE III

2-Substituted Benzimidazoles



		Reflux Period	Yield %	m.p. °C	Literature m.p. °C	Reference
H	*p* $CH_3OC_6H_4$	3 hr. 5 min.	90 60	231-233 (c)	228	(16)
H	C_6H_5	3 hr.	90	299-301 (a)	291	(17)
H	*p* ClC_6H_4	5 hr.	73	299-301 (b)	294	(17)
H	*p* FC_6H_4	4 hr.	84	260-264 (a)	258	(18)
5(6)Cl	C_6H_5	3 hr.	44	216-218 (a)	210	(17)
H	$-CH_2C_6H_5$	4 hr.	42	189-190 (a)	188-189	(17)
H		4 hr.	55	283-285 (a)	285-286	(17)
H		4 hr.	97	243-245 (a)	245	(3)
H		5 hr.	21	229-231 (b)	224-226	(19)
H	*p* $NO_2C_6H_4$	5 hr. 5 min.	19 13	290 (c)	298-299	(4)

(a) From ethanol. (b) From dimethylformamide/ethanol. (c) From 2-propanol.

A mixture of *o*-phenylenediamine (24.5 g., 0.23 mole) and the bisulfite adduct of benzaldehyde (60.7 g., 0.288 mole) in 150 ml. of ethanol was boiled under reflux for 3 hours, then evaporated. The solid residue was recrystallized from ethanol to give 38.5 g., (90%) of 2-phenylbenzimidazole with m.p. 299-300° which gave no depression on admixture with a specimen prepared according to the method of Jerchel (3).

When the reflux period was reduced to 5 or 15 minutes, yields were 50% and 72% respectively.

Prepared in the same manner, with a reflux period of 5 minutes, were 2-phenylperimidine hydrochloride; yield 98%, m.p. 237-239° from 0.2 *N* hydrochloric acid solution (Sachs (14) gives m.p. 240°) and 1,3,8-trimethylxanthine picrate; yield 62%, m.p. 190° from water.

Anal. Calcd. for $C_{14}H_{13}N_7O_9$: N, 23.2. Found: N, 23.8.

The base gave no depression of the m.p. on admixture with a specimen prepared according to the method of Speer (15).

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(1) Smith Kline and French Labs. Ltd. All enquiries should be addressed to H.F.R.

(2a) Chester Beatty Research Institute. (b) This investigation has been supported in part (G.M.T.) by a grant to the Chester Beatty Research Institute (Institute Cancer Research; Royal Cancer Hospital) from the Medical Research Council and the British Empire Cancer Campaign for research and by the U. S. Public Health Services Research grant No. CA-03188-08 from the National Cancer Institute.

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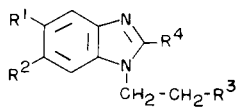
TABLE IV

1:2-Disubstituted Benzimidazoles



R^1	R^2	R^3	R^4	Reflux Period	Yield %	m.p.°C	Literature m.p.°C	Formula	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found	% Nitrogen Calcd.	% Nitrogen Found	Ultraviolet Spectra in Ethanol λ	ε	λ	ε
H	Cl	$-N(CH_3)_2$	C_6H_5	3 hr.	50	105-108 (a)	-	$C_{17}H_{18}ClN_3$	68.1	68.3	6.05	6.30	14.0	13.7	293.0	16,110	253.7	7,840
H	Cl	$-N(CH_3)_2$	*p* ClC_6H_4	3 hr.	54	136-138 (a)	-	$C_{17}H_{17}Cl_2N_3$	61.1	61.1	5.13	5.23	12.6	12.4	293.5	18,520	256.0	9,740
Cl	H	$-N(CH_3)_2$	C_6H_5	3 hr.	47	54-55 (d)	-	$C_{17}H_{16}ClN_3$	68.1	67.9	6.05	6.29	14.0	14.0	294.5	12,690	252.7	7,440
CF_3	H	$-N(CH_3)_2$	C_6H_5	2 hr.	69	200-203 (c)	-	$C_{18}H_{18}F_3N_3 \cdot HCl$	58.5	58.7	5.18	5.20	11.36	11.36	285.5	13,170	251.0	7,050
CF_3	H	$-N(CH_2CH_3)_2$	C_6H_5	5 hr.	31	237-238 (c)	-	$C_{20}H_{22}F_3N_3 \cdot 2HCl$	55.3	54.9	5.57	5.82	9.7	9.5	286.5	15,250	251.5	8,070
H	H	-OH	C_6H_5	5 min.	74	150 (b)	152-153 (f)	$C_{15}H_{14}N_2O$	-	-	-	-	-	-	-	-	-	-
H	H	-OH	*p* $CH_3OC_6H_4$	5 min.	54	159 (e)	-	$C_{16}H_{16}N_2O_2$ $C_6H_5N_3O_7$	53.1	53.7	3.85	3.80	14.1	13.8	-	-	-	-
H	H	-OH	CH_3	5 min.	79	150 (b)	151-152 (f)	$C_{10}H_{12}N_2O$	-	-	-	-	-	-	-	-	-	-

(a) From 2-propanol. (b) From benzene. (c) From ethanol. (d) From petroleumether. (e) From water. (f) Reference (20).

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