200° (0.3 mm). Colorless crystals, mp 97–98°, were obtained on crystallizing from ligroin (bp 75–120°).

α-Isopropyl-α-(4-dimethylaminobutyl)-1-naphthylacetic Acid Hydrochloride (XIII).—XII (32.6 g, 0.1 mole) was treated with isoamyl nitrite (40.7 ml) in glacial acetic acid (163 ml) and in the presence of anhydrous HCl, as described for III. A colorless product, mp 239–240°, was obtained on crystallization from ethanol–ligroin (bp 75–120°).

Pharmacology.—The acute toxicity and hypoglycemic activity were investigated by the techniques previously described;[4a] chlorpropamide was used as standard. The data are listed in Table II.

Acknowledgments.—The authors thank Mr. O. Boniardi for his assistance in preparing the compounds, Dr. G. Sekules for the microanalyses, and Mr. E. Pavesi for the pharmacological tests.

Substituted 2-(5-Nitro-2-furyl)benzimidazoles

P. M. C. BAVIN

Smith Kline and French Laboratories Ltd., Mundells, Welwyn Garden City, Hertfordshire, England

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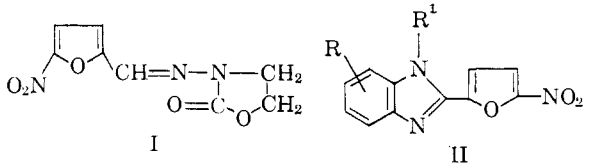
Although many nitrofurans show *in vitro* and *in vivo* activity against *Trichomonas* species, only 3-[(5-nitrofurfurylidene)amino]-2-oxazolidone (I) has undergone extensive clinical trials.[1,2] 2-(5-Nitro-2-furyl)benzimidazole (IIa), prepared in these laboratories during the evaluation of a synthetic method,[3] was shown to have activity against *T. foetus* in the mouse of an order sufficient to warrant investigation of related compounds.[4]



I

II

	R	R¹
a	H	H
b	5(6)-Cl	H
c	H	CH_2CH_2OH
d	5,6-$(CH_3)_2$	H
e	H	CH_3
f	5-CF_3	CH_2CH_2OH
g	5,6-Cl_2	H
h	H	$CH_2CH_2N(CH_3)_2$
i	H	C_6H_5
j	5(6)-CO_2CH_3	H
k	5-CF_3	$CH_2CH_2N(C_2H_5)_2$

The parent compound IIa had a short duration of activity in the mouse, probably because of rapid metabolism. It seemed unlikely that the benzimidazole ring was involved directly in the activity[6] but rather that it served to transport the nitrofuryl residue, which is well known to exhibit a wide range of antimicrobial ac-

TABLE I
SUBSTITUTED 2-(5-NITRO-2-FURYL)BENZIMIDAZOLES

	R	R¹	Cryst. solvent	Mp, °C	Yield,[a] %	Formula	Calcd, % C	H	N	Cl	Found, % C	H	N	Cl
a	H	H	DMF–methanol	230–231[b]	81	$C_{11}H_7N_3O_3$			18.3				18.05	
b	5(6)-Cl	H	Methanol	236–237	46	$C_{11}H_6ClN_3O_3$	50.1	2.29	15.9	13.45	49.7	2.21	16.2	13.7
c	H	CH_2CH_2OH	DMF–methanol	206–207	69	$C_{13}H_{11}N_3O_4$	57.1	4.06			57.35	4.31		
d	5,6-$(CH_3)_2$	H	Ethyl acetate	285–287	66	$C_{13}H_{11}N_3O_3$	60.7	4.31	16.4		60.4	4.37	16.7	
e	H	CH_3	Acetone–ethanol	218–219.5[c]	9	$C_{12}H_9N_3O_3$	59.3	3.73	17.3		59.3	4.13	17.45	
f	5-CF_3	CH_2CH_2OH	Ethanol	219–220	25	$C_{14}H_{10}F_3N_3O_4$	49.3	2.95	12.3		49.1	3.14	12.4	
g	5,6-Cl_2	H	DMF–ethanol	308–310	17	$C_{11}H_5Cl_2N_3O_3$	44.3	1.69	23.8		44.1	2.02	23.55	
h	H	$CH_2CH_2N(CH_3)_2$	Methanol	140–142	35	$C_{15}H_{16}N_4O_3$	60.0	5.37	18.7		60.2	5.29	18.55	
i	H	C_6H_5	Acetonitrile	244–245	57	$C_{17}H_{11}N_3O_3$	66.9	3.63	13.8		66.7	3.39	13.9	
j[d]	5(6)-CO_2CH_3	H	Chloroform–ethanol	248–250	25	$C_{13}H_9N_3O_5$	54.4	3.16	14.6		54.3	3.43	14.8	
k	5-CF_3	$CH_2CH_2N(C_2H_5)_2$	DMF–methanol	124–125	15	$C_{15}H_{16}F_3N_4O_3$	54.55	4.83	14.1		54.3	4.95	14.2	

[a] Yields refer to analytically pure material and are not maximal. [b] Lit. mp 223–231°,[3] 224–226°,[5] 223–224°;[6] analytical data have not been recorded previously. [c] Lit.[3] mp 213–214°; analytical data have not been recorded previously. [d] The crude acid was too insoluble for crystallization and was esterified with diazomethane in methanol–$CHCl_3$ suspension.

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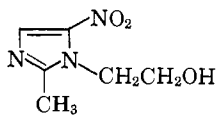
TABLE II

ANTITRICHOMONAL ACTIVITY (AGAINST *T. Foetus*) OF 2-(5-NITRO-2-FURYL)BENZIMIDAZOLES (II) COMPARED WITH METRONIDAZOLE

II	R	R^1	*In vitro*	*In vivo*[a] Sc	*In vivo*[a] Oral
a	H	H	1.0[b]	1.0	1.0
b	5(6)-Cl	H	0.04	*c*	2.0
c	H	CH_2CH_2OH	0.06	1.0	1.0
d	5,6-$(CH_3)_2$	H	0.03	1.0	1.0
e	H	CH_3	0.1	1.0	1.0
f	5-CF_3	CH_2CH_2OH	0.05	1.0	*c*
g	5,6-$(Cl)_2$	H	0.01	2.0–4.0	>2.0
h	H	$CH_2CH_2N(CH_3)_2$	0.05	1.0	*c*
i	H	C_6H_5	*d*	*d*	*d*
j	5(6)-CO_2CH_3	H	0.015	1.0	1.0

[a] Administered subcutaneously in 5 daily doses against a lethal (intraperitoneal) *T. foetus* infection in the mouse. [b] Results are expressed as ratio of MIC (minimum inhibitory concentration) of compound to metronidazole (III) (Flagyl®), *i.e.*, dose necessary to produce the same effect as metronidazole which had MIC of 0.20 g/ml.[5] [c] Not done. [d] Too insoluble.

tivities. In order to limit possible metabolism of the benzimidazole ring, the substituted compounds IIb, IId, IIf, IIg, and IIk were prepared. The strong bases IIh and IIk were prepared to facilitate transport, having in mind the weakly acidic character of vaginal tissues.[2] The alcohols IIc and IIf were prepared in order to examine the effect of a solubilizing group (*cf.* 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (III)).

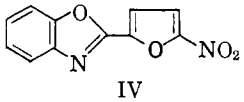


III

Most of the compounds were more active than III against *T. foetus in vitro*, but showed only comparable activity against subcutaneous infections of *T. foetus* in the mouse. Analytical and biological data are summarized in Tables I and II.

Although derivatives of nitrofuran are used to treat coccidiosis, the present compounds were inactive against *Eimeria tenella* in 3–4-week-old chicks.[7]

The original preparation[3] of 2-(5-nitro-2-furyl)benzimidazole (IIa) and methods published during the course of this work[8] were not suitable for large-scale preparations. An alternative synthesis of benzimidazoles[9] employing the condensation of methyl- (or ethyl-) 5-nitro-2-furimidate[10] with a substituted *o*-phenylenediamine in water-free alcohol containing hydrogen chloride gave excellent yields of II and IV and had the added advantage of wide generality (*cf.* ref 5). Since the completion of this work, IIa and IIc have been reported,[11] prepared by the same procedure.



IV

Experimental Section

Melting points were recorded using an Electrothermal gas-heated apparatus equipped with a thermometer calibrated for stem exposure. Microanalyses were carried out by Mr. M. Graham.

Intermediates.—5-Nitro-2-furonitrile was prepared by dehydrating 5-nitro-2-furfuraldehyde oxime with acetic anhydride[12,13] and converted to the methyl or ethyl imidate hydrochloride in the usual way.[14]

o-Phenylenediamine was recrystallized before use. *o*-Aminodiphenylamine was purchased from Koch Laboratories, and *o*-phenylenediamine-4-carboxylic acid from Koch–Light Laboratories. 4-Chloro-*o*-phenylenediamine was purchased from Fluka Chemical Co. and 4,5-dichloro- and 4,5-dimethyl-*o*-phenylenediamine from Aldrich Chemical Co. N-Methyl-*o*-phenylenediamine was prepared by methylating *o*-phenylenediamine with methyl iodide[15] but thin layer chromatography (benzene–ether on silica, developed with Dragendorf's reagent or potassium iodoplatinate) showed three substances to be present, thereby accounting for the low yield of IIe.

N-(2-Hydroxethyl)-*o*-nitroaniline, prepared by condensing ethanolamine with *o*-chloronitrobenzene in the presence of pyridine, had mp 74–75° (lit.[16] mp 76°). Reduction with hydrazine and palladized charcoal in ethanol gave N-(2-hydroxyethyl)-*o*-phenylenediamine, mp 108–110° (lit.[16] mp 107°), used for the preparation of IIc.

N-(2-Dimethylaminoethyl)-*o*-nitroaniline was prepared by condensing N,N-dimethylethylenediamine with *o*-chloronitrobenzene in boiling xylene in the presence of K_2CO_3.[17] The crude basic product was reduced with hydrazine and palladized charcoal in ethanol to give N-(2-dimethylaminoethyl)-*o*-phenylenediamine,[11] used for the preparation of IIh.

N-(2-Hydroxethyl)-2-nitro-4-trifluoromethylaniline was prepared by heating 4-chloro-3-nitrobenzotrifluoride (189 g, 0.84 mole) with ethanolamine (135 g, 2.2 moles) in boiling pyridine (150 g) for 16 hr. Excess chloro compound was removed by steam distillation and the residue was cooled and extracted with ether. Evaporation followed by crystallization from chloroform–hexane gave orange prisms (56 g, 26.7%), mp 60–62°.

Anal. Calcd for $C_9H_9F_3N_2O_3$: C, 42.9; H, 3.60. Found: C, 43.2; H, 3.60.

N¹-(2-Hydroxethyl)-4-trifluoromethyl-*o*-phenylenediamine was prepared by reducing the nitroamine (10 g) with hydrazine and Pd–C in ethanol. The diamine separated from chloroform as colorless plates (4.5 g, 52%), mp 98–99°, used for the preparation of IIf.

Anal. Calcd for $C_9H_{11}F_3N_2O$: C, 49.1; H, 5.08; N, 12.7. Found: C, 49.0; H, 5.16; N, 12.9.

N¹-(2-Diethylaminoethyl)-4-trifluoromethyl-*o*-phenylenediamine was prepared in the usual way[17] by Ridley, *et al.*,[3] who provided a generous sample for the preparation of IIk.

2-(5-Nitro-2-furyl)benzimidazoles.—In a typical experiment, a solution of recrystallized *o*-phenylenediamine (3.24 g, 0.03

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mole) and ethyl 5-nitro-2-furimidate hydrochloride (6.6 g, 0.03 mole) in methanol (20 ml, previously dried by distillation from sodium methoxide–diethyl oxalate) was warmed for 1 hr. Dilution with hot water (15 ml) induced crystallization of small yellow prisms (6.0 g, 81%) mp 230–231° (lit.[8] mp 224–226°). The product ran as a single spot on alumina developed with benzene.

The other benzimidazoles were prepared similarly, as yellow to orange crystalline solids. In many cases they crystallized directly from the methanol. All products were examined by thin layer chromatography on alumina and purified until they ran as a single spot.

2-(5-Nitro-2-furyl)benzoxazole crystallized from DMF–methanol as yellow needles (63%), mp 231–232° (lit.[8] mp 225–227°).

New Compounds

The Synthesis of Tertiary Arylalkylamines from Aryl Grignard Reagents

P. M. G. BAVIN, C. R. GANELLIN, J. M. LOYNES, P. D. MILES, AND H. F. RIDLEY

Smith Kline and French Laboratories Ltd., Welwyn Garden City, Hertfordshire, England

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The arylalkyl tertiary amines are an important class of compounds in medicinal chemistry which contain drugs effective as antihistamines, spasmolytics, tranquilizers, and antidepressants. We now report that the reaction of aryl Grignard reagents with dialkylaminoalkyl chlorides provides a useful general procedure for the synthesis of arylalkylamines. The method is exemplified with phenyl, 1-naphthyl, 9-phenanthryl, 3-indenyl, and 3-benzo[*b*]thienylmagnesium bromides. It is also applicable to indole,[1] 2,5-diphenylfuran,[2] and 3-phenylindene.[3] A similar use of aryllithium compounds is illustrated by 2-benzo[*b*]-thienyllithium.

Experimental Section[4]

N,N-Dimethylphenethylamine Hydrochloride.—A dry solution of 2-dimethylamino-1-chloroethane (0.2 mole)[5] in toluene (100 ml) was added to the Grignard reagent from bromobenzene (32 g, 0.2 mole) in ether (100 ml). The mixture was heated under reflux for 1 hr and then poured onto ice and an excess of HCl. The aqueous layer was separated off, washed with toluene, then made alkaline with NaOH, and extracted with ether. Evaporation of the dried ethereal extracts left the amine as an oil (7.2 g) which was converted into its hydrochloride. The latter was crystallized from 2-propanol–ether mixture to yield 5.0 g (13.4%) of colorless needles, mp 166–167°, lit.[6] mp 171°.

Anal. Calcd for $C_{10}H_{16}ClN$: C, 64.8; H, 8.7; N, 7.5. Found: C, 64.5; H, 8.4; N, 7.5.

N,N-Dimethyl-3-phenylpropylamine hydrochloride was prepared similarly from phenylmagnesium bromide (0.2 mole) and 3-dimethylamino-1-chloropropane (0.4 mole). It was crystallized from 2-propanol–ether mixture and obtained in 13% yield (5.2 g). The hydrochloride was extremely hygroscopic and the product was characterized by its **hydrogen oxalate,** mp 131–133° (from ethyl methyl ketone), and **picrate,** mp 96–98°, lit.[7] mp 99°.

Anal. Calcd for $C_{11}H_{17}N \cdot C_2H_2O_4$: C, 61.6; H, 7.6; N, 5.5. Found: C, 61.9; H, 7.8; N, 5.5.

Anal. Calcd for $C_{11}H_{17}N \cdot C_6H_3N_3O_7$: C, 52.0; H, 5.1; N, 14.3. Found: C, 52.2; H, 5.0; N, 14.1.

N,N-Dimethyl-2-(9-phenanthryl)ethylamine Hydrochloride.—In a similar manner 2-dimethylamino-1-chloroethane (0.05 mole) in toluene (50 ml) was added to the Grignard reagent from 9-bromophenanthrene (12.9 g, 0.05 mole) in ether–benzene (30:30 ml) and the stirred mixture was heated under reflux for 2 hr. The hydrochloride, after crystallization from 2-propanol–ether mixture, yielded 1.5 g (10.5%) of colorless needles, mp 228–230°.

Anal. Calcd for $C_{18}H_{20}ClN$: C, 75.6; H, 7.1; N, 4.9. Found: C, 75.7; H, 7.3; N, 4.6.

N,N-Dimethyl-3-(9-phenanthryl)propylamine hydrochloride was prepared similarly from 9-phenanthrylmagnesium bromide (0.05 mole) and 3-dimethylamino-1-chloropropane (0.05 mole). It was obtained in 7.3% yield (1.1 g) as colorless needles (from 2-propanol–ether), mp 220–222°.

Anal. Calcd for $C_{19}H_{22}ClN$: C, 76.2; H, 7.4; N, 4.7. Found: C, 76.4; H, 7.3; N, 4.6.

N,N-Dimethyl-2-(1-naphthyl)ethylamine Hydrochloride.—A dry solution of 2-dimethylamino-1-chloroethane (0.5 mole) in toluene (150 ml) was added slowly, during 90 min, to the Grignard reagent from 1-bromonaphthalene (52 g, 0.25 mole) in ether–benzene (150:150 ml); the reaction was sufficiently exothermic to maintain reflux without additional heating. The mixture was stirred overnight at room temperature in an atmosphere of nitrogen and then worked up to afford 4.1 g of the amine, as an oil, which was converted into its hydrochloride. The latter was crystallized first from ethanol–ether mixture and then from ethanol to yield 2.5 g (4.2%) of colorless microcrystalline needles, mp 214–215°, lit.[8] mp 213°.

Anal. Calcd for $C_{14}H_{18}ClN$: C, 71.3; H, 7.7; N, 5.9. Found: C, 71.1; H, 7.4; N, 5.9.

N,N-Dimethyl-2-(3-indenyl)ethylamine Hydrochloride.—Ethylmagnesium bromide (1.0 mole) was prepared in diethyl ether (200 ml) and the solvent was then displaced by dry toluene (700 ml). A solution of indene (116 g, 1.0 mole) in toluene (100 ml) was added dropwise during 1 hr to the stirred mixture at 95° in an atmosphere of nitrogen, and the temperature was maintained at 95–100° for a further 10 hr. After being cooled to room temperature the solvent was decanted from the pale yellow solid indenyl Grignard reagent[9] and the latter was then washed with two 200-ml portions of dry toluene and suspended in anhydrous ether (700 ml). To this suspension was added a dry solution of 2-dimethylaminoethyl-1-chloroethane (1.0 mole) in ether (500 ml) during 30 min. The reaction was sufficiently exothermic to maintain reflux without additional heating and after a further 2 hr the mixture was poured onto crushed ice and aqueous NH_4Cl. The oily amine (99.9 g) was isolated and converted into its hydrochloride which, after being crystallized from 2-propanol, was obtained as colorless needles (79.4 g, 35.6%), mp 175–177.5°.

Anal. Calcd for $C_{13}H_{18}ClN$: C, 69.8; H, 8.1; N, 6.3. Found: C, 69.6; H, 8.1; N, 6.5.

N,N-Dimethyl-2-(3-benzo[*b*]thienyl)ethylamine Hydrogen Oxalate.—A dry solution of 2-dimethylaminoethyl-1-chloroethane (0.2 mole) in toluene (100 ml) was added to 3-benzo[*b*]-thienylmagnesium bromide[10] [from 21.3 g (0.1 mole) of 3-bromo-

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(4) Melting points were recorded using an Electrothermal® melting point apparatus comprising a gas-heated block and a thermometer calibrated for stem exposure. Microanalyses are by Mr. M. J. Graham (Smith Kline and French Laboratories Ltd.). The purity and identity of all products were confirmed by thin layer chromatography, and ultraviolet and infrared absorption spectra.
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