587. *The Synthesis of some Perfluoroalkylbenzimidazoles.*

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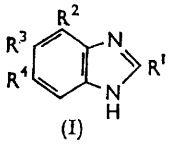
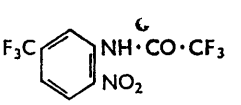
Perfluoroalkylbenzimidazoles have been synthesised either by condensation of an *o*-diamine with a carboxylic acid, or by reduction of an *N*-(*o*-nitrophenyl)perfluoroalkanamide with concomitant cyclisation of the *o*-amino-derivative. 2-Trifluoromethylbenzimidazole-4-carboxylic acid was obtained by oxidation of the 4-methyl compound, 2-carboxylic acids by oxidation of 2-hydroxymethyl compounds, and 2-amino-derivatives by the action of cyanogen bromide on *o*-diamines.

Syntheses of 4,5-bistrifluoromethyl-, 2-methyl-4,5-bistrifluoromethyl-, and 2,4,5-tristrifluoromethyl-benzimidazoles have been reported.[1,2] The finding that these compounds had appreciable antibacterial activity *in vitro* led to the synthesis of a number of new perfluoroalkylbenzimidazoles and their derivatives in order to correlate chemical structure with antibacterial activity. The synthetic work is now reported.

The benzimidazoles (I) listed in Table 1 were synthesised by the condensation of known *o*-diamines with carboxylic acids in the presence of strong acids. In general the yields of the 2-heptafluoropropyl derivatives were lower than those of the 2-trifluoromethyl derivatives, and these were lower than those of 2-methyl or 2-hydroxymethyl derivatives. This trend can be ascribed to steric hindrance by the comparatively bulky perfluoroalkyl groups. The use of stronger acid than hitherto[1-3] resulted in increased yields or shorter reaction times for the formation of the known perfluoroalkylbenzimidazoles.



(I)



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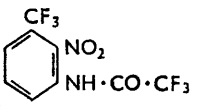


(III)

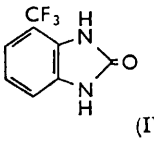
An alternative method of synthesis was by hydrogenation of an *N*-(*o*-nitrophenyl)-alkanamide, when reduction of the nitro-group and cyclisation to the benzimidazole occurred in one stage. Thus, *N*-(2-nitro-5-trifluoromethylphenyl)trifluoroacetamide (II), obtained by the action of trifluoroacetic anhydride on 3-amino-4-nitrobenzotrifluoride, was hydrogenated in the presence of Raney nickel to give 2,5-bistrifluoromethylbenzimidazole (I; $R^1 = R^3 = CF_3$, $R^2 = R^4 = H$) in 60% yield (from the 3-amino-compound, cf. 48% yield by previous method [2]). 4-Methyl-2-trifluoromethyl-, 2-heptafluoropropyl-4-methyl-, and 5-methoxy-2-trifluoromethyl-benzimidazole were obtained similarly by reducing *N*-(2-methyl-3-nitrophenyl)trifluoroacetamide, *N*-(2-methyl-3-nitrophenyl)heptafluorobutyramide, and *N*-(4-methoxy-2-nitrophenyl)trifluoroacetamide, respectively (Table 3). However, the trifluoroacetamide (III) was reduced to the 2-amino-compound, which did not cyclise. A possible explanation of this is that the hydrogen atoms of the 2-amino-group are hydrogen-bonded to the fluorine atoms. Also *N*-(4,5-dimethyl-2-nitrophenyl)-trifluoroacetamide and *N*-(4-methoxy-2-nitrophenyl)heptafluorobutyramide were reduced to the corresponding amines which did not cyclise. The reason why the former failed to cyclise is obscure since the expected product, 5,6-dimethyl-2-trifluoromethylbenzimidazole (I; $R^1 = CF_3 = R^2 = H$, $R^3 = R^4 = Me$), was formed by the reaction of 4,5-diamino-*o*-xylene with trifluoroacetic acid.

2-Trifluoromethylbenzimidazole-4-carboxylic acid was obtained by oxidation of the

[1] Sykes and Tatlow, *J.*, 1952, 4078.
[2] Belcher, Sykes, and Tatlow, *J.*, 1954, 4159; Fernandez-Bolaños, Overend, Sykes, Tatlow, and Wiseman, *J.*, 1960, 4003.
[3] Smith and Steinle, *J. Amer. Chem. Soc.*, 1953, **75**, 1292; Lane, *J.*, 1955, 534.

4-methyl compound, and 4- and 5-trifluoromethylbenzimidazole-2-carboxylic acids from the corresponding 2-hydroxymethyl derivatives which were obtained by condensation of the appropriate *o*-diamine with glycollic acid. The 2-carboxylic acids were easily decarboxylated, even on recrystallisation, and analyses were therefore not satisfactory. The acids were characterised by means of their infrared spectra and decarboxylation products.

2-Amino-derivatives of benzimidazole were obtained by condensation of *o*-diamines with cyanogen bromide.[4] This procedure was applied to the synthesis of 2-amino-4-trifluoromethyl- and 2-amino-5-trifluoromethyl-benzimidazole. Attempts to convert the 2-amino-derivatives into 2-nitro-derivatives, by oxidation with either trifluoroperacetic acid or Caro's acid, were unsuccessful. Attempts were made, therefore, to obtain a 2-nitro-



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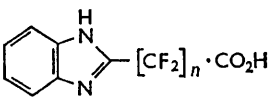

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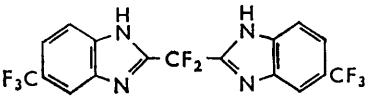

(VI)

derivative by the action of sodium nitrite on diazotised 2-amino-4-trifluoromethylbenzimidazole, but the product was 4-trifluoromethylbenzimidazol-2(3*H*)-one (IV).

Benzimidazole derivatives were also obtained by the condensation of *o*-diamines with fluorine-containing dibasic acids. Thus, equimolar proportions of *o*-phenylenediamine and difluoromalonic acid gave benzimidazol-2-yldifluoroacetic acid (V; $n = 1$). Similarly, tetrafluorosuccinic acid gave β-benzimidazol-2-yltetrafluoropropionic acid (V; $n = 2$). Two molar proportions of 3,4-diaminobenzotrifluoride to one of difluoromalonic acid gave difluorobis-(5-trifluoromethylbenzimidazol-2-yl)methane (VI).

The benzimidazoles were characterised from their elemental analyses, infrared spectra,[5] and, in most cases, ultraviolet spectra. Their antibacterial properties are described elsewhere.[6]

Experimental

o-*Diamines*.—2,3- and 3,4-diaminobenzotrifluoride were obtained by Sykes and Tatlow's method.[1] The other diamines were obtained commercially or prepared by established procedures.

Condensation of o-*Diamines with Carboxylic Acids*.—The diamine and an excess of the carboxylic acid were heated for 3 hr. at 100° with 10N-hydrochloric acid. The solution was neutralised, and the benzimidazole which separated was filtered off and recrystallised. The results are shown in Table 1.

Reductive Cyclisation of N-(o-*Nitrophenyl*)*perfluoroalkanamides*.—The *N*-(*o*-nitrophenyl)-perfluoroalkanamides in Table 2 were prepared by the action of either boiling trifluoroacetic anhydride or perfluorobutyric anhydride at 100° on the appropriate *o*-nitro-amines. The products were hydrogenated at 4 atm. at 20° for 90 min. in ethanol with Raney nickel catalyst (activity W-2) [2] to give the benzimidazoles in Table 3. The structures of these were confirmed by infrared spectroscopy. When no benzimidazole was formed the product was probably an amino-compound. Attempts to cyclise these with strong acids failed.

2-*Trifluoromethylbenzimidazole*-4-*carboxylic acid*.—Potassium permanganate (250 mg.) in water (10 ml.) was slowly added to a well-stirred suspension of 4-methyl-2-trifluoromethylbenzimidazole (160 mg.) in water (25 ml.) at 50—60°. The temperature was raised to 100° and the mixture stirred for 1 hr, cooled, acidified, and decolourised with sulphur dioxide. The solution was extracted continuously with ether, and the extract was dried and evaporated to dryness, giving the *acid* (50 mg., 27%), m. p. 250—254° (from benzene) (Found: C, 47·0; H, 2·4%; Equiv., 235. $C_9H_5F_3N_2O_2$ requires C, 47·0; H, 2·2%; Equiv., 230).

4-*Trifluoromethylbenzimidazole*-2-*carboxylic acid*.—2-Hydroxymethyl-4-trifluoromethylbenzimidazole (0·4 g.) was treated with potassium permanganate (0·6 g.) at 100°, as described above.

[4] Pellizzari and Gaiter, *Gazzetta*, 1918, **48**, II, 151; Leonard, Curtin, and Beck, *J. Amer. Chem. Soc.*, 1947, **69**, 2459.
[5] Morgan, *J.*, 1961, 2343.
[6] Biship, Chelton, and Jones, *Biochem. Pharmacol.*, 1964, **13**, 751.

TABLE 1.

Preparation and properties of perfluoroalkylbenzimidazoles.

Benzimidazoles (I)				Wt. of	Wt. of	10N-HCl	Solvent for	Yield		Found (%)							
R^1	R^2	R^3	R^4	diamine (g.)	acid (g.)	(ml.)	cryst.	(%)	M. p.	C	H	F			C	H	F
C_2F_5	H	H	H	2·0	5·0	0·5	EtOH–H_2O	45	212—214°	46·1	2·0	40·0	Calc. for $C_9H_5F_5N_2$		45·8	2·1	40·2
CF_3	CF_3	H	H	2·0	9·6	1·0	EtOH–H_2O	62	151—152								
CF_3	H	CF_3	H	2·0	9·6	0·5	EtOH–H_2O	48	198—200								
C_3F_7	H	H	H	0·3	4·25	0·5	EtOH–H_2O	30	220	41·8	1·6	—	,,	$C_{10}H_5F_7N_2$	42·0	1·8	—
CF_3	H	NO_2	H	1·0	3·5	0·5	H_2O	40	152—154	41·9	1·7	24·2	,,	$C_8H_4F_3N_3O_2$	41·6	1·7	24·7
C_3F_7	H	CF_3	H *	0·45	4·25	0·2	C_6H_6	9	172—173	37·2	1·6	52·8	$C_{11}H_4F_{10}N_2$	requires	37·3	1·1	53·7
C_3F_7	CF_3	H	H *	1·5	7·5	2·5	C_6H_6	17	143	37·5	1·2	53·6	$C_{11}H_4F_{10}N_2$	,,	37·3	1·1	53·7
Me	H	CF_3	H	1·0	2·0	0·5	EtOH–H_2O	70	183·5—184·5	54·0	3·8	28·8	$C_9H_7F_3N_2$	,,	54·0	3·5	28·5
C_3F_7	H	NO_2	H †	1·0	5·0	0·5	C_6H_6	4·2	174—176	35·3	1·6	—	$C_{10}H_4F_7N_3O_2,\frac{1}{2}H_2O$	,,	35·3	1·5	—
CF_3	Me	H	H	0·8	1·5	0·5	C_6H_6	60	143—145	53·6	3·7	28·8	$C_9H_7F_3N_2$	,,	54·0	3·5	28·5
CF_3	H	Me	Me	0·3	1·5	0·5	C_6H_6	22	232—234	56·3	4·5	—	$C_{10}H_9F_3N_2$	,,	56·1	4·2	—
CF_3	Me	Me	H	0·4	1·5	0·5	C_6H_6	12	153—154	56·9	4·3	—	$C_{10}H_9F_3N_2$	,,	56·1	4·2	—
CHF_2	CF_3	H	H	0·5	0·5	3·0	light petroleum	15	154—156	46·0	2·0	40·8	$C_9H_5F_5N_2$	,,	45·8	2·1	40·2
CF_3	H	Cl	H	1·0	3·0	15 ‡	C_6H_6	71	198—200	43·3	2·0	25·6	$C_8H_4ClF_3N_2$	,,	43·5	1·8	25·8
C_3F_7	H	Cl	H	1·5	5·0	15 ‡	C_6H_6	44	156—157	37·7	1·4	—	$C_{10}H_4ClF_7N_2$	,,	37·5	1·3	—
CF_3	4,5-Benzo §			1·0	6·0	15 ‡	C_6H_6	53	172—174	61·2	2·7	—	$C_{12}H_7F_3N_2$	,,	61·0	3·0	—
$-CH_2\cdot OH$	CF_3	H	H	1·0	1·0	5·0	H_2O	82	190—191	50·1	3·3	26·1	$C_9H_7F_3N_2O$	,,	50·0	3·3	26·4
$-CH_2\cdot OH$	H	CF_3	H	0·5	0·5	2·5	H_2O	65	228—230 (d.)	49·9	3·3	26·4	$C_9H_7F_3N_2O$	,,	50·0	3·3	26·4

* Reaction carried out under nitrogen. † Heated at 170° for 15 hr. in sealed tube; alumina chromatography used to purify the product. ‡ 4N-HCl used.
§ *I.e.*, a naphthimidazole.

TABLE 2.

N-(*o*-Nitrophenylperfluoroalkanamides.

Amides	Yield (%)	M. p.	Found (%) C	H	F	Formula	Required (%) C	H	F
N-(2-Nitro-5-trifluoromethylphenyl)trifluoroacetamide	83	47—48°	35·7	1·3	37·3	$C_9H_4F_6N_2O_3$	35·8	1·3	37·8
N-(2-Methyl-6-nitrophenyl)trifluoroacetamide	97	128—129	43·3	2·8	22·7	$C_9H_7F_3N_2O_3$	43·5	2·8	22·9
N-(2-Methyl-6-nitrophenyl)heptafluorobutyramide	71	63—64	38·3	1·7	—	$C_{11}H_7F_7N_2O_3$	37·9	2·0	—
N-(2-Methoxy-6-nitrophenyl)trifluoroacetamide	87	92—94	41·2	2·6	21·4	$C_9H_7F_3N_2O_4$	40·9	2·7	21·6
N-(2-Nitro-3-trifluoromethylphenyl)trifluoroacetamide *	88	127—129	35·8	1·2	37·8	$C_9H_4F_6N_2O_3$	35·8	1·3	37·8
N-(4,5-Dimethyl-2-nitrophenyl)trifluoroacetamide *	78	81—82	45·9	4·3	21·4	$C_{10}H_9F_3N_2O_3$	45·8	3·5	21·7
N-(4-Methoxy-2-nitrophenyl)heptafluorobutyramide *	65	64—65	36·9	1·9	—	$C_{11}H_7F_7N_2O_4$	36·3	1·9	—

* Did not cyclise to a benzimidazole on reduction.

TABLE 3.

Perfluoroalkylbenzimidazoles.

Benzimidazole	Yield (%)	M. p.	Found (%) C	H	F		C	H	F
2,4-Bistrifluoromethyl	72	198—199°	42·5	1·4	44·8	Calc. for $C_9H_4F_6N_2$	42·5	1·6	44·9
4-Methyl-2-trifluoromethyl	71	143—144	53·6	3·7	28·7	$C_9H_7F_3N_2$ requires	54·0	3·5	28·5
2-Heptafluoropropyl-7-methyl	56	179—180	44·4	2·8	43·8	$C_{11}H_7F_7N_2$ requires	44·0	2·3	44·3
5-Methoxy-2-trifluoromethyl	65	144—146	50·2	3·3	—	$C_9H_7F_3N_2O$ requires	50·0	3·2	—

After acidification, and removal of manganese dioxide with sulphur dioxide, the clear solution was kept at 4° for 15 hr. The resulting precipitate was filtered off, to give the acid (0·3 g., 57%), m. p. 115—120° (decomp.) (from water) solidifying and remelting at 192—193°. This compound did not give the correct analysis because it could not be dried without decomposition (for evidence for its structure from infrared data see ref. 5). A sample, when heated at its melting point, gave 4-trifluoromethylbenzimidazole, m. p. 192—193° (lit.,[1] 192—195°) (Found: C, 51·7; H, 2·7; F, 30·3. Calc. for $C_8H_5F_3N_2$: C, 51·6; H, 2·7; F, 30·6%).

5-*Trifluoromethylbenzimidazole-2-carboxylic acid*.—2-Hydroxymethyl-5-trifluoromethylbenzimidazole (0·22 g.) was oxidised with potassium permanganate (0·32 g.), as described above. The product (0·18 g., 72%), m. p. 150—151°, could not be crystallised without decomposition. Its infrared spectrum [5] indicated that it was a benzimidazole-2-carboxylic acid. Sublimation gave 6-trifluoromethylbenzimidazole, m. p. 117—119° (lit.,[1] 119°) (Found: C, 51·4; H, 2·4%).

2-*Amino-6-trifluoromethylbenzimidazole*.—A suspension of 3,4-diaminobenzotrifluoride (2 g.) in water (20 ml.) was treated with cyanogen bromide (1·2 g.) [7] with shaking. After all the cyanogen bromide had been added, the mixture was shaken for 30 min., kept at 15° for 15 hr, made alkaline with dilute ammonia, and kept at 4° for a few hours. The solid was filtered off, to give the amino-compound (1·5 g., 65%), m. p. 156—158°. This compound could not be recrystallised satisfactorily and did not sublime. However, when its ethereal solution was treated with trifluoroacetic anhydride in the usual way, N-(5-*trifluoromethylbenzimidazol-2-yl*)*trifluoroacetamide monohydrate* was obtained, m. p. 232—233° (decomp.) (from water) (Found: C, 38·1; H, 2·4. $C_{10}H_5F_6N_3O,H_2O$ requires C, 38·1; H, 2·2%). This compound decomposed when attempts were made to remove the water of crystallisation.

2-*Amino-4-trifluoromethylbenzimidazole*.—2,3-Diaminobenzotrifluoride (2 g.) was treated with cyanogen bromide (1·2 g.) as described above, to give the *amino-compound* (1·3 g., 60%), m. p. 154—156° (from benzene) (Found: C, 47·6; H, 3·5; F, 28·7. $C_8H_6F_3N_3$ requires C, 47·7; H, 3·0; F, 28·3%). This compound, on treatment with trifluoroacetic anhydride, gave N-(4-*trifluoromethylbenzimidazol-2-yl*)*trifluoroacetamide monohydrate*, m. p. 238—240° (decomp.) (from water) (Found: C, 38·4; H, 2·3. $C_{10}H_5F_6N_3O,H_2O$ requires C, 38·1; H, 2·2%).

Attempted Conversion of the 2-Aminotrifluoromethylbenzimidazoles into 2-Nitro-compounds.—(*a*) 2-Amino-6-trifluoromethylbenzimidazole was treated with trifluoroperacetic acid in boiling dichloromethane for 24 hr., to give *N*-(5-trifluoromethylbenzimidazol-2-yl)trifluoroacetamide, m. p. and mixed m. p. 230—233°.

(*b*) 2-Amino-4-trifluoromethylbenzimidazole was treated at 40° with Caro's acid (prepared by adding ice-cold sulphuric acid to potassium persulphate) for 4 hr. The product was the sulphate of the starting material.

(*c*) A cooled solution of 2-amino-4-trifluoromethylbenzimidazole (0·58 g.) in glacial acetic acid (6 ml.) was added slowly to a cooled solution of sodium nitrite in concentrated sulphuric acid (2 ml.). After stirring for 1 hr., dry ether (50 ml.) was added, and the resulting precipitate filtered off, washed with glacial acetic acid then ether, and added to a suspension of cuprous sulphate (from cupric sulphate, 5 g.) in a solution of sodium nitrite (10 g.) in water (40 ml.). The mixture was stirred for 2 hr. and extracted with ether for 15 hr. The ethereal solution was evaporated to dryness, to give 4-*trifluoromethylbenzimidazol-2*(3*H*)-*one*, m. p. 270—272° (from benzene) (Found: C, 47·2; H, 2·6. $C_8H_5F_3N_2O$ requires C, 47·6; H, 2·5%).

Benzimidazol-2-yldifluoroacetic Acid.—An intimately ground mixture of *o*-phenylenediamine (0·54 g.) and difluoromalonic acid (0·78 g.) was heated at 170° for 5 min. The mixture was cooled, triturated with 4N-ammonia (25 ml.), and filtered, and the filtrate was acidified and extracted for 15 hr. with ether. The ethereal extract was evaporated to dryness, to give the *acid hemihydrate* (0·58 g., 55%), m. p. 163—164° (decomp.) (from water) (Found: C, 48·7; H, 3·3%; Equiv, 228. $C_9H_6F_2N_2O_2\frac{1}{2}H_2O$ requires C, 48·8; H, 3·2%; Equiv, 230).

β-*Benzimidazol-2-yltetrafluoropropionic Acid*.—*o*-Phenylenediamine (0·2 g.) was treated with tetrafluorosuccinic acid and the product isolated, as for the previous experiment, to give the *acid monohydrate* (0·2 g., 39%), m. p. 255—256° (from water) (Found: C, 42·9; H, 2·7. $C_{10}H_6F_4N_2O_2,H_2O$ requires C, 42·8; H, 2·9%).

Difluorobis-(5-*trifluoromethylbenzimidazol-2-yl*)*methane*.—A mixture of 3,4-diaminobenzotrifluoride (0·8 g.) and difluoromalonic acid (0·93 g.) was heated at 150° for 5 min., cooled, and dissolved in a little acetone. 4N-Ammonia (50 ml.) was added, the mixture was filtered, and the

[7] *Org. Synth.*, Coll. Vol. III, 1955, p. 662.

filtrate acidified and extracted with ether (5 × 25 ml.). The ether extract was evaporated, leaving an oil which crystallised from water to give the *difluoromethane monohydrate* (0·13 g., 14%), m. p. 156—158° (Found: C, 46·5; H, 2·6. $C_{17}H_8F_8N_4,H_2O$ requires C, 46·6; H, 2·3%). There was no acidic group titratable in the range expected for a carboxyl group.

Infrared Spectra.—Some of these have been discussed elsewhere.[5] The spectra of the other benzimidazoles were characteristic, showing a broad band at about 2600 cm.$^{-1}$, due to a hydrogen bond of the type NH • • • N, and a series of three or four bands in the region 1500—1630 cm.$^{-1}$. The absence of a strong band at 1600—1650 cm.$^{-1}$ showed that the compounds were not amides. The spectrum of 4-trifluoromethylbenzimidazol-2(3*H*)-one showed a strong band at 1700 cm.$^{-1}$ which was presumably due to the C=O group.

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