Highly Fluorinated Analogues of Pharmacologically Active Compounds

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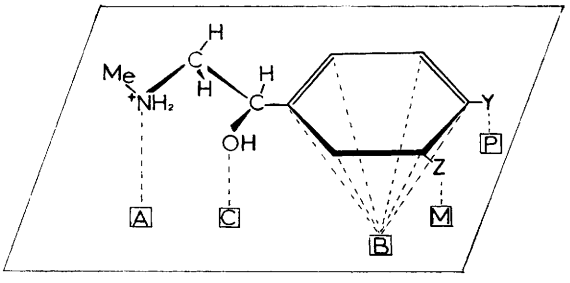
The pentafluorophenyl analogues of noradrenaline, adrenaline, and *N*-methyladrenaline [$C_6F_5 \cdot CH(OH) \cdot CH_2 \cdot NR^1R^2$ with $R^1 = R^2 = H$; $R^1 = H$, $R^2 = Me$; $R^1 = R^2 = Me$, respectively] have been prepared by reduction with sodium borohydride of the corresponding amino-ketones obtained by standard methods. 3-(*N*-2-Chloroethyl-*N*-ethyl)-aminomethyl-4,5,6,7-tetrafluorobenzo[*b*]thiophen has also been synthesised as a potential catecholamine antagonist and anti-tumour agent, by a method involving the cyclisation with polyphosphoric acid of 2,3,4,5-tetrafluorophenylthiopropanone to give the expected 4,5,6,7-tetrafluoro-3-methylbenzo[*b*]thiophen, and thence by standard methods. The above pentafluorophenyl compounds are only very weak catecholamine antagonists.

As PENTAFLUOROBENZENE derivatives became more readily available, it was interesting to speculate about the changes in pharmacological activity which would result from the replacement of the catechol residue of adrenaline and related compounds by the pentafluorophenyl group. The current picture [1] of the catecholamine α-receptor has a site B to accommodate the aromatic ring (see Figure), and two sites, P and M,



The adrenaline or catecholamine α-receptor

which accommodate the catecholic hydroxyl groups. These sites appear more or less equally important in determining the strength of attachment of the drug to the receptor site, and it may be that upon the introduction of the pentafluorophenyl group, any decrease in attraction to site B because of the reduced basicity of the aromatic ring would be counterbalanced by an increased attraction of the more electronegative fluorine substituents for sites P and M. The pentafluorophenyl analogues of adrenaline, noradenaline, and *N*-methyladrenaline were therefore prepared for pharmocological evaluation.

Previous preparations [2] of 2,3,4,5,6-pentafluoro-benzaldehyde and -acetophenone have made use of 2,3,4,5,6-pentafluorophenyl magnesium bromide or iodide. With the ready availability of 2,3,4,5,6-pentafluorobenzoic acid, we decided to use this as starting material. The acid was converted into the acid chloride and thence into the amide as described by Tatlow and his co-workers,[3] but the overall yield was raised to 87%. Dehydration of the amide with phosphorus pentoxide at 200° gave the corresponding nitrile in 54% yield. 2,3,4,5,6-Pentafluoroacetophenone was prepared (61%) by the action of methyl magnesium iodide on this nitrile in tetrahydrofuran; also (56%) by the action of dimethylcadmium on 2,3,4,5,6-pentafluorobenzoyl chloride. If the reaction of the Grignard reagent with the nitrile was carried out in ether, the reaction mixture exploded violently when the organometallic complex was decomposed with dilute aqueous acid.

The substituted acetophenone reacted with bromine in ether to give the corresponding phenacyl bromide (88%), which was reduced with aqueous sodium borohydride; the product was treated with 2N-potassium hydroxide to give 2,3,4,5,6-pentafluorostyrene oxide (75%). Because of the strongly electron-withdrawing

[1] (*a*) B. Belleau, *Canad. J. Biochem. Physiol.*, 1958, **36**, 731; (*b*) N. B. Chapman, K. Clarke, and R. D. Strickland, *Proc. Roy. Soc.*, 1965, *B*, **163**, 116.

[2] E. Nield, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 1959, 166.

[3] A. K. Barbour, M. W. Buxton, P. L. Coe, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 1961, 808.

properties of the pentafluorophenyl group, the reaction of this epoxide with an amine should give only the "normal" isomer, *i.e.*, the secondary amino-alcohol (cf. Parker and Isaacs' Review [4]). The epoxide reacted with dimethylamine in a sealed tube to give the required 2-hydroxy-2-(2,3,4,5,6-pentafluorophenyl)-*NN*-dimethylethylamine (79%). Similarly, ammonia or methylamine yielded the crude primary or secondary amino-alcohol, which could not be purified and so were characterised as the hydrochloride and maleate, respectively. The structures of these amino-alcohols were confirmed by their infrared and nuclear magnetic resonance spectra, and for the primary amino-compound, by independent synthesis.

2,3,4,5,6-Pentafluorobenzonitrile was reduced with anhydrous stannous chloride in ethereal hydrogen chloride to give the corresponding aldehyde in 62% yield. Condensation of this aldehyde with nitromethane, even under conditions normally expected to produce nitrostyrenes, gave only the nitro-alcohol, which was very difficult to purify. The presence of the alcoholic hydroxyl group was clearly indicated by the infrared spectrum, and furthermore the crude nitro-alcohol was reduced with lithium aluminium hydride in ether to give a specimen of 2-hydroxy-2-(2,3,4,5,6-pentafluorophenyl)ethylamine identical with that obtained from 2,3,4,5,6-pentafluorostyrene oxide. Tatlow and his co-workers [3] found that the Knoevenagel reaction of 2,3,4,5,6-pentafluorobenzaldehyde with malonic acid in pyridine gave rise to a hydroxy-acid which could be dehydrated with concentrated sulphuric acid. Our findings confirm that the hydroxy-compound which is produced from the carbonyl compound during such condensations is considerably stabilised by the presence of the powerfully electron-withdrawing pentafluorophenyl group.

The variation in pharmacological activity caused by replacing the aromatic ring of a known adrenaline antagonist by a fluorinated ring was also investigated. 3-(*N*-2-Chloroethyl-*N*-ethyl)aminomethylbenzo[*b*]thiophen hydrochloride has been shown[5] to produce a complete blockade of the α-receptor sites of adrenaline, and more recently, unlike other α-blockers, to possess noticeable anti-tumour activity,[6] and so the 4,5,6,7-tetrafluoro-derivative was prepared. 2,3,4,5-Tetrafluorothiophenol was condensed with chloroacetone and the resulting thiopropanone was cyclised by heating it with polyphosphoric acid at 160—180° to give 4,5,6,7-tetrafluoro-3-methylbenzo[*b*]thiophen (74%). Bromination with *N*-bromosuccinimide in carbon tetrachloride gave the 3-bromomethyl derivative (58%) which was condensed with *N*-ethylethanolamine. The resulting amino-alcohol (91%) was isolated as its hydrochloride, which was then halogenated by boiling it with thionyl chloride in dry chloroform.

Administered intravenously to the spinal rat 2-hydroxy-2-pentafluorophenylethylamine hydrochloride appeared inactive against the pressor effect of adrenaline or noradrenaline, whereas the *N*-mono- or -di-methyl derivative showed very weak activity. The first compound, however, showed weak activity in the acute rat preparation. 3-(*N*-2-Chloroethyl-*N*-ethyl)aminomethyl-4,5,6,7-tetrafluorobenzo[*b*]thiophen still awaits pharmacological evaluation.

EXPERIMENTAL

2,3,4,5,6-Pentafluorobenzoic acid was donated by the Imperial Smelting Corporation, Avonmouth. As the work progressed, 2,3,4,5,6-pentafluoro-benzonitrile and -acetophenone also became available.

The acid was converted into the acid chloride (90%) by the action of phosphorus pentachloride at 100° for 1 hr., and then was converted into the amide (97%) by treatment with ammonia as described by Tatlow *et al.*[3]

2,3,4,5,6-*Pentafluorobenzonitrile*.—A mixture of 2,3,4,5,6-pentafluorobenzamide (6·3 g., 0·03 mole) and phosphorus pentoxide (8·6 g., 0·06 mole) was heated to 200°. A colourless oil distilled over, b. p. 184—188°, which was redistilled under reduced pressure to give a product of b. p. 69—71°/12 mm. (lit.,[7] 185—190°/760 mm.), yield 3·1 g. (54%).

2,3,4,5,6-*Pentafluorobenzaldehyde*.—Dry hydrogen chloride was passed into a stirred suspension of anhydrous stannous chloride (13·5 g., 0·075 mole) in dry ether (200 ml.), until the mixture formed two layers, the lower viscous layer being a solution of stannous chloride in ethereal hydrogen chloride. 2,3,4,5,6-Pentafluorobenzonitrile (9·7 g., 0·05 mole) was added to this mixture with vigorous stirring, whereupon a white precipitate was deposited. This was filtered off and hydrolysed with warm water, and the resulting aldehyde was extracted with ether and the ethereal solution was dried (Na_2SO_4). The ether was removed and the residue was distilled under reduced pressure to give the product as a yellow oil, b. p. 50—54°/10 mm. (lit.,[3] 168—170°/760 mm.), yield 4·1 g. The filtrate which remained after the white precipitate had been filtered off was evaporated to dryness, the residue was hydrolysed with warm water, and the product was extracted with ether and dried (Na_2SO_4). Distillation gave a further 2·0 g. of 2,3,4,5,6-pentafluorobenzaldehyde. Total yield 6·1 g. (62%).

2,3,4,5,6-Pentafluorobenzaldehyde 2,4-dinitrophenylhydrazone had m. p. 227—228° (lit.,[3] 229—230°) (Found: C, 41·6; H, 1·6; N, 15·3. Calc. for $C_{13}H_5F_5N_4O_4$: C, 41·5; H, 1·3; N, 14·9%).

2,3,4,5,6-*Pentafluoroacetophenone*.—(*a*) *From 2,3,4,5,6-pentafluorobenzoyl chloride*. A solution of methyl bromide (19·1 g., 0·2 mole) in dry ether (50 ml.) was added to an ice-cold, stirred suspension of magnesium (4·9 g., 0·2 mole) in dry ether (50 ml.) at such a rate that the ether boiled gently. After the mixture had been stirred at room temperature for 1 hr., anhydrous cadmium chloride (18·3 g., 0·1 mole) was added to the refluxing Grignard solution, and the mixture was stirred for 30 min. A test [8] was carried out at this stage to ensure that all the Grignard reagent had reacted. The ether was removed and replaced by an equal volume of dry benzene. 2,3,4,5,6-Pentafluorobenzoyl

[4] R. E. Parker and N. S. Isaacs, *Chem. Rev.*, 1959, **59**, 737.
[5] J. D. P. Graham, *J. Med. Pharm. Chem.*, 1960, **2**, 499.
[6] K. Hellman, P. G. Marshall, and S. Stayt, *Brit. J. Pharmacol.*, in the press.
[7] W. J. Pummer and L. A. Wall, *J. Res. Nat. Bur. Stand.*, 1959, **63***A*, 167; U.S.P. 3,046,313.
[8] H. Gilman and J. F. Nelson, *Rec. Trav. chim.*, 1936, **55**, 518.

chloride (18·4 g., 0·08 mole) was added to the boiling benzene solution, which was then heated under reflux for 2 hr. The complex was decomposed by pouring the reaction mixture on to ice, and sufficient 2N-sulphuric acid was added to dissolve the white precipitate formed. Ether was added, the organic layer was separated, and the aqueous layer was shaken with more ether. The extracts were dried (Na_2SO_4), the solvents were removed, and the residue was distilled to give the product as a colourless oil of b. p. 54—56°/5 mm., yield 9·4 g. (56%) (Found: C, 45·9; H, 1·7. Calc. for $C_8H_3F_5O$: C, 45·8; H, 1·4%). *2,3,4,5,6-Pentafluoroacetophenone 2,4-dinitrophenylhydrazone* (from ethanol) had m. p. 157—158° (Found: C, 43·2; H, 2·1; N, 14·0. $C_{14}H_7F_5N_4O_4$ requires: C, 43·1; H, 1·8; N, 14·4%). *2,3,4,5,6-Pentafluoroacetophenone semicarbazone* (from ethanol) had m. p. 214—215° (Found: C, 40·0; H, 2·5; N, 16·0. $C_9H_6F_5N_3O$ requires: C, 40·4; H, 2·3; N, 15·7%).

(*b*) *From 2,3,4,5,6-pentafluorobenzonitrile.* (i) A solution of methyl iodide (21·3 g., 0·15 mole) in dry ether (50 ml.) was added slowly to an ice-cold, stirred suspension of magnesium (3·7 g., 0·15 mole) in dry ether (50 ml.), and the mixture was stirred at room temperature for 1 hr. This solution was again cooled in ice, and a solution of 2,3,4,5,6-pentafluorobenzonitrile (9·8 g., 0·05 mole) in dry ether (50 ml.) was added slowly. When the addition was complete, the ether was removed and the resulting red viscous liquid was stirred at 100° for 1 hr. The complex was suspended in ether and the mixture was poured into ice-cold dilute sulphuric acid. Decomposition occurred with explosive violence. (ii) The above procedure was modified by using dry tetrahydrofuran instead of ether as the solvent, and the complex was decomposed gently by pouring it into wet tetrahydrofuran. The product was extracted with ether, washed with water, and dried (Na_2SO_4). The ether was removed, and the residue was distilled under reduced pressure to give a colourless oil of b. p. 51—53°/2·5 mm., yield 6·4 g. (61%).

2,3,4,5,6-Pentafluorophenacyl Bromide.—Bromine (8·0 g., 0·05 mole) was added slowly to an ice-cold stirred solution of 2,3,4,5,6-pentafluoroacetophenone (10·5 g., 0·05 mole) in dry ether (200 ml.). The colour of the bromine rapidly disappeared to leave an orange-yellow solution, which was washed with water, then with sodium carbonate solution, finally with water, and dried (Na_2SO_4). The ether was removed and the solid product was recrystallised from light petroleum (b. p. 40—60°). It had m. p. 30—32°, yield 13·2 g. (88%) (Found: C, 33·6; H, 1·1; Br, 27·5. $C_8H_2BrF_5O$ requires: C, 33·3; H, 0·7; Br, 27·7%).

2,3,4,5,6-Pentafluorostyrene Oxide.—A solution of sodium borohydride (1·6 g., 0·05 mole) in a mixture of water (16 ml.) and 2N-sodium hydroxide (2 ml.) was added to a stirred solution of 2,3,4,5,6-pentafluorophenacyl bromide (11·6 g., 0·04 mole) in dioxan (100 ml.), and the mixture was stirred at room temperature for 1 hr. It was acidified with 2N-sulphuric acid (50 ml.), poured into water, and shaken with di-isopropyl ether. The extracts were added to 2N-potassium hydroxide (50 ml.), and the mixture was stirred at 60° for 15 min. Stirring was continued for a further 30 min. without heating, and the product was extracted with ether and dried (Na_2SO_4). The ether was removed and the residue was distilled to give the product as a colourless oil of b. p. 70—72°/15 mm., yield 6·3 g. (75%) (Found: C, 45·9; H, 1·7; $C_8H_3F_5O$ requires: C, 45·8; H, 1·4%).

2-Hydroxy-2-(2,3,4,5,6-pentafluorophenyl)-NN-dimethylethylamine.—2,3,4,5,6-Pentafluorostyreneoxide (3·2 g., 0·015 mole) and dimethylamine (2·7 g., 0·06 mole) in dry benzene were heated in a sealed tube at 120° for 2 hr. The product was distilled under reduced pressure to give a colourless oil of b. p. 112—116°/1 mm., which solidified when kept at room temperature for 12 hr. It was recrystallised from light petroleum (b. p. 80—100°) as colourless needles of m. p. 96—97°, yield 2·0 g. (79%) (Found: C, 47·3; H, 3·6; N, 5·2. $C_{10}H_{10}F_5NO$ requires: C, 47·1; H, 3·9; N, 5·5%).

2-Hydroxy-2-(2,3,4,5,6-pentafluorophenyl)-N-methylethylamine was prepared similarly, but could not be obtained pure and was therefore characterised as the maleate, m. p. 124—125° (Found: C, 42·3; H, 3·3; N, 3·9. $C_{13}H_{12}F_5NO_5$ requires: C, 42·5; H, 3·3; N, 3·8%).

2-Hydroxy-2-(2,3,4,5,6-pentafluorophenyl)ethylamine was prepared similarly and had m. p. 100—103°. It could not be obtained pure, and was therefore characterised as the hydrochloride, m. p. 212—213° (Found: C, 36·7; H, 2·7; N, 5·3. $C_8H_7ClF_5NO$ requires: C, 36·4; H, 2·7; N, 5·3%).

Condensation of 2,3,4,5,6-Pentafluorobenzaldehyde with Nitromethane.—(*a*) A solution of 2,3,4,5,6-pentafluorobenzaldehyde (3·0 g., 0·015 mole) and nitromethane (1·0 g., 0·015 mole) in methanol (100 ml.) was cooled to 0°, and a solution of sodium hydroxide (0·70 g., 0·016 mole) in water (20 ml.) was added dropwise, the temperature being kept below 15°. After 30 min., the solution was poured slowly into a large excess of 2N-hydrochloric acid, and the resulting white solid was filtered off. Repeated crystallisation from several solvents failed to give a pure compound, but the infrared spectrum was strongly indicative of the nitro-alcohol structure.

(*b*) A solution of 2,3,4,5,6-pentafluorobenzaldehyde (2·0 g.) in glacial acetic acid (10 ml.) was heated under reflux for 2 hr. in the presence of nitromethane (1·0 g.) and ammonium acetate (200 mg.). Water was added dropwise to the cold mixture, and a brown oil was deposited. The oil could not be distilled, but the product was obtained as a solid by dissolution in ether and evaporation of the solvent. The infrared spectrum of this waxy solid was very similar to that of the product described in (*a*).

Reduction of the nitro-alcohol. The crude nitro-alcohol (3·0 g.) in dry ether (50 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (1·0 g., 100% excess) in dry ether (100 ml.), and the mixture was then heated under reflux for 5 hr. Water was added cautiously to decompose the excess of lithium aluminium hydride, followed by 2N-sodium hydroxide (100 ml.). The ethereal layer was separated, dried ($MgSO_4$), and dry hydrogen chloride was passed into the dry solution. The resulting solid was collected and recrystallised from anhydrous ethanol as white plates, m. p. 212—213°, yield 2·3 g. The product was identical with the hydrochloride of the amine prepared from 2,3,4,5,6-pentafluorostyrene oxide.

2,3,4,5-Tetrafluorophenylthiopropanone.— Chloroacetone (12·5 g., 0·135 mole) was added dropwise to a stirred solution of 2,3,4,5-tetrafluorothiophenol (24·2 g., 0·133 mole) in sodium hydroxide solution (5·3 g., 0·133 mole in 150 ml. water), the temperature being maintained between 20 and 25°. Stirring was continued for another hour at room temperature and the heavy oil which separated was extracted with ether, washed with water, and dried (Na_2SO_4). The ether was removed and the residual liquid was distilled under reduced pressure, b. p. 94—96°/3 mm., yield 23·7 g.

(85%). The semicarbazone, prepared in the usual manner and recrystallised from ethanol, had m. p. 188—189° (Found: C, 41·3; H, 3·4; N, 13·95. $C_{10}H_9F_4N_3OS$ requires C, 41·05; H, 3·5; N, 14·2%). The 2,4-dinitrophenylhydrazone was prepared in the usual way. Crystallisation from ethanol gave yellow needles of m. p. 106—107° (Found: N, 13·3. $C_{15}H_{10}F_4N_4O_4S$ requires N, 13·4%).

4,5,6,7-*Tetrafluoro*-3-*methylbenzo*[b]*thiophen*.— 2,3,4,5-Tetrafluorophenylthiopropanone (42 g., 0·175 mole) was added slowly to vigorously stirred polyphosphoric acid (400 g.) preheated to 160°. The temperature was maintained at 160—180° for 2 hr. and then the brown reaction mixture was cooled and poured into cold water. The product was extracted with ether, washed with water, and dried (Na_2SO_4). The ether was removed and the resulting oil was distilled under reduced pressure, and had b. p. 80°/2 mm., yield 28·5 g. (74%). Crystallisation from light petroleum (b. p. 40—60°) gave colourless needles of m. p. 62—63° (Found: C, 49·1; H, 1·5; F, 34·8. $C_9H_4F_4S$ requires C, 49·1; H, 1·8; F, 34·5%).

4,5,6,7-*Tetrafluoro*-3-*methylbenzo*[b]*thiophen* 1,1-*Dioxide*.—Hydrogen peroxide (10 ml. of a 28% aqueous solution) was added to a solution of 4,5,6,7-tetrafluoro-3-methylbenzo[*b*]thiophen (1·0 g.) in glacial acetic acid (15 ml.). The mixture was heated on a steam-bath for 1 hr., cooled, and poured into water (100 ml.). The dioxide separated as a white solid which was filtered off, washed with water, and crystallised from ethanol. It had m. p. 117—118°, yield 0·7 g. (64%) (Found: C, 43·1; H, 1·3; F, 30·1. $C_9H_4F_4O_2S$ requires C, 42·8; H, 1·6; F, 30·0%).

3-*Bromomethyl*-4,5,6,7-*tetrafluorobenzo*[b]*thiophen*.—Benzoyl peroxide (1 g.) was added to a rapidly stirred solution of 4,5,6,7-tetrafluoro-3-methylbenzo[*b*]thiophen (22 g., 0·1 mole) in dry carbon tetrachloride (250 ml.). *N*-Bromosuccinimide (18 g., 0·1 mole) was added in small portions to the boiling mixture, which was also irradiated by two 200-w electric light bulbs. After being boiled and stirred for a further 2 hr., the mixture was cooled to 0°, the succinimide was filtered off, and the carbon tetrachloride was distilled off under reduced pressure. The residual oil on being cooled deposited colourless crystals which were collected, recrystallised from light petroleum (b. p. 40—60°), and had m. p. 66—68°, yield 17·4 g. (58%) (Found: C, 36·4; H, 1·4; Br, 26·8. $C_9H_3BrF_4S$ requires C, 36·1; H, 1·0; Br, 26·7%).

3-(N-*Ethyl*-N-2-*hydroxyethyl*)*aminomethyl*-4,5,6,7-*tetrafluorobenzo*[b]*thiophen Hydrochloride*.—A solution of 3-bromomethyl-4,5,6,7-tetrafluorobenzo[*b*]thiophen (12 g., 0·04 mole) and *N*-ethylethanolamine (7·2 g., 0·08 mole) in dry benzene (150 ml.) was boiled under reflux for 2 hr. Dry ether (150 ml.) was added to the cold reaction mixture and the *N*-ethylethanolamine hydrobromide which separated was filtered off. The filtrate was washed thoroughly with water and dried (Na_2SO_4). The solvent was removed and the crude reaction product was converted into its hydrochloride by dissolving it in dry ether and adding slowly with shaking, a solution of hydrogen chloride in dry ether. The hydrochloride separated as a viscous mass which slowly solidified; the white solid was filtered off, washed with dry ether, and dried. Yield 12·5 g. (91%). Crystallisation from ethyl methyl ketone gave white prisms, m. p. 131—133° (Found: C, 45·8; H, 4·0; N, 4·25. $C_{13}H_{14}ClF_4NOS$ requires C, 45·4; H, 4·1; N, 4·1%).

3-(N-2-*Chloroethyl*-N-*ethyl*)*aminomethyl*-4,5,6,7-*tetrafluorobenzo*[b]*thiophen Hydrochloride*.—A stirred suspension of 3-(*N*-ethyl-*N*-2-hydroxyethyl)aminomethyl-4,5,6,7-tetrafluorobenzo[*b*]thiophen hydrochloride (8·6 g., 0·025 mole) in dry chloroform (200 ml.) was heated under reflux until the solid completely dissolved. Thionyl chloride (6·0 ml., 9·6 g., 0·08 mole) was then added dropwise and heating was continued for a further 1·5 hr. The removal of all volatile material gave a solid which was washed thoroughly with dry ether and recrystallised from ethyl methyl ketone as white needles, m. p. 158—160°, yield 8·5 g. (94%) (Found: C, 42·7; H, 3·8; N, 4·1. $C_{13}H_{13}Cl_2F_4NS$ requires C, 43·1; H, 3·6; N, 3·9%).

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