Synthesis and EPR Investigations of Fluorocatecholamines

Hartmut B. Stegmann,* Gabriele Deuschle and Paul Schuler
Institut für Organische Chemie der Universität Tübingen, Auf der Morgenstelle 18, D-720 76 Tübingen, Germany

The synthesis of 3-fluoro- and 5-fluoronoradrenaline (3- and 5-fluoronorepinephrine) starting from 4-fluorophenol or 3-fluoroanisole is described. In the first step the second OH group is introduced followed by *O*-methylation and subsequent introduction of an acetyl function by Friedel–Crafts acylation. Replacement of one acetyl proton by bromine and reaction with potassium phthalimide yields the adrenalone-type compounds. After cleavage of the methyl ethers and hydrazinolysis of the amide function the catecholamines were obtained by reduction of the carbonyl group.

Oxidation of the catechols obtained by the reduction leads to the corresponding semiquinone radicals which gave rise to well resolved EPR and, in some cases, ENDOR spectra. An assignment of the data obtained could be made by comparison of the variety of radicals investigated and with the help of multiresonance experiments. The 5-fluoro-*o*-benzosemiquinones are less stable than the 3-fluoro-radicals as can be seen by the formation of paramagnetic secondary products.

Fluorinated organic compounds are of great biochemical interest.[1] The usual strategy for their preparation is the introduction of one or two fluorine atoms as one of the final steps.[2] This technique is essential when ^{18}F compounds for PET (positron emission tomography) investigations are prepared.[3] In all other cases the fluorine substitution can be done at an early synthetic stage. Nowadays a variety of fluorine compounds are commercially available and, therefore, the modification of these starting materials provides an alternative pathway. Furthermore, this concept has the advantage of enabling a number of catecholamines and derivatives to be synthesised from one starting substance. Catecholamines and the related catechols are redox-active compounds. After the introduction of a fluoro atom in the aromatic moiety an alteration in these properties is expected. For this reason, the monovalent oxidation of the compounds, their spin-density distribution and the chemical reactions have been investigated which might be of biological interest.

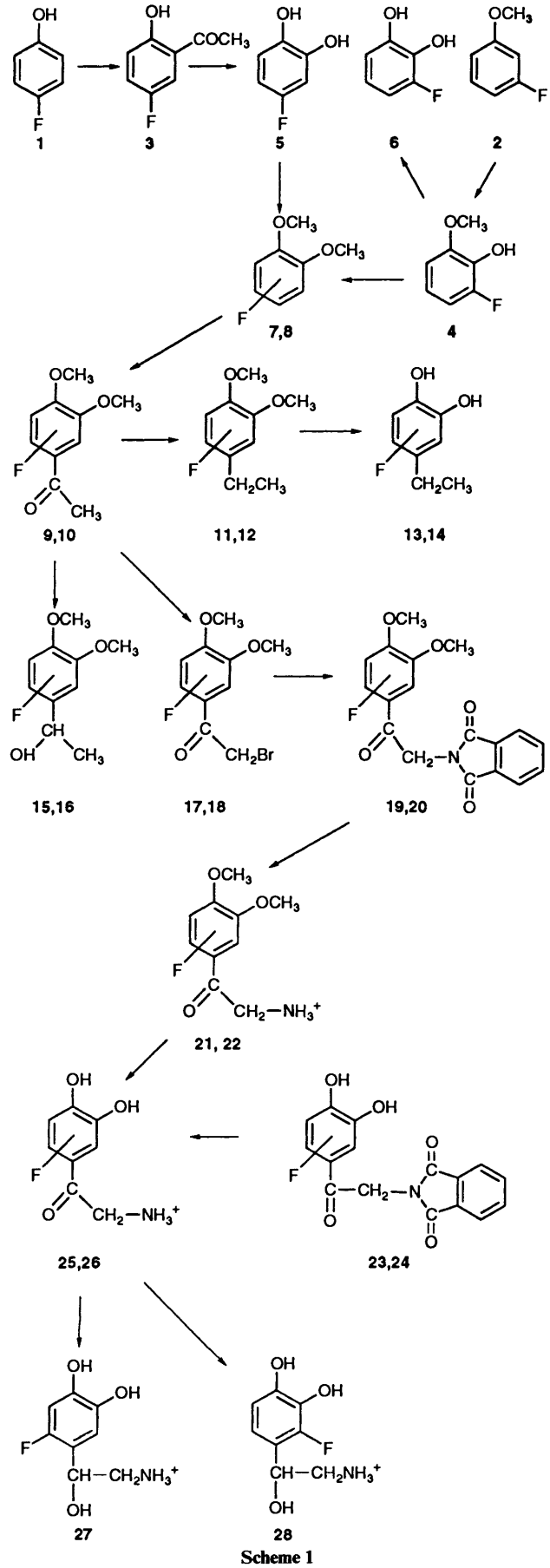
Synthesis of Veratroles, Catechols and Catecholamines.—The starting material for preparation of 5-fluoroadrenalone **25** and all other compounds labelled with odd numbers was the 4-fluorophenol **1** (Scheme 1). This compound is commercially available. Reaction of **1** with acetic anhydride yields the ketone **3** and upon subsequent oxidation the 4-fluorocatechol **5**[4] is formed. The compounds labelled with even numbers were prepared from 3-fluoroanisole **2** which led finally to the noradrenaline **28**. The guaiacol **4** was prepared according to the literature.[5,6] Cleavage of the methyl ethers yielded the catechol **6**. Both phenols, **5** and **4**, can be converted into the corresponding veratroles **7** and **8** by alkylation as already described in the literature.[5,7] Veratrole **7** can also be purchased from Aldrich. The structure of all compounds prepared were confirmed by ^1H and ^{13}C NMR spectra. These data were mostly not available for the known compounds but the knowledge is helpful for the interpretation of spectra of the new compounds. Comparison of **7** and **8** shows that the methoxy protons and the methoxy carbon in *ortho*-position to the fluorine atom exhibit a doublet splitting in the ^1H as well as in the ^{13}C spectra. Comparable splittings are also observed in the methyl ethers derived from **a**, **b** and **c**, and therefore this long-range coupling is very useful for the assignment of the fluorine position in the compounds under investigation.

The veratroles **7** and **8** react with acetyl chloride to give the corresponding ketones **9** and **10** in good yields. This reaction can likewise be performed with the dimethoxy derivative of **a** but with poorer yields. The new compounds were characterized by ^1H and ^{13}C NMR as well as by IR and mass spectroscopy. The ^1H NMR spectrum of **10** shows the splitting of one methoxy group by the fluorine atom in the *ortho*-position as expected. In both ketones, **9** and **10**, an isotropic magnetic interaction of the ^{19}F nucleus with the methyl protons of the acetyl group is observed. The coupling constant is *ca.* 5.5 Hz for both compounds. This value is too large for a regular $^5J_{H,F}$ long-range splitting. Therefore, a through-space interaction must be invoked,[8] as already mentioned by Schaefer *et al.*[9] for 2-fluoroacetophenone, in accordance with the coplanar conformation of the molecules. These interpretations are confirmed by the ^{13}C NMR spectra. The absorptions of the methyl carbons in the side chain of **9** and **10** are split by an interaction with the fluorine atom into doublets (8.6 and 7.5 Hz). The experimental and theoretical aspects of those couplings are discussed thoroughly in the literature.[10,11] The mass spectra show the molecular ion peak and a simple fragmentation; both have a base peak due to $M^+ - CH_3$.

The cleavage of the OCH_3 bonds could not be achieved for **9** and **10**, or for the acetyl compound derived from **a**. Obviously, these bonds are drastically deactivated owing to the different electron-withdrawing substituents in these molecules. Therefore, the reduction products were prepared in order to investigate the ether cleavage in the compounds of interest.

Reduction of **9** and **10** with $NaBH_4$ in CH_3OH leads to the corresponding alcohols **15** and **16** in very good yields. However, demethylation to the catechols was unsatisfactory under all conditions applied. The reaction products were dark oils consisting of a variety of compounds as indicated by thin layer chromatography. Reduction with palladium-on-charcoal proceeded smoothly and yielded the ethyl veratroles **11** and **12** which were converted into the corresponding catechols **13** and **14** by treatment with boron tribromide in methylene chloride.[12] The yields were approximately 90% in both cases. In the ^1H NMR spectra, the methyl groups are shifted to higher field and have a triplet structure due to the interaction with the methylene protons. A long-range coupling with the fluorine atoms could not, in this case, be detected because the proposed conformational requirements in the carbonyl

* Fax: 07071 29 52 46.



Scheme 1

compounds **9** and **10** disappear after the reduction. These results are consistent with those of the ^{13}C NMR spectra. Thus, the NMR investigations combined with IR and mass spectra confirmed the structures given for the ethyl compounds.

These results indicate that cleavage of the ethers could be carried out after reduction of the ketone function. Therefore, the strategy used seems to be successful at least in the case of the ethyl compounds. For this reason, we continued the synthesis by introduction of bromine into the compounds **9** and **10**, leading to **17** and **18** in order to create a substituent with the capability of undergoing nucleophilic substitution by a nitrogen moiety. The bromoacetyl compounds **17** and **18** were obtained in good yields and were straightforwardly characterized by NMR and mass spectroscopy.

Reaction of **17** and **18** with hexamethylenetetramine yields the corresponding ammonium salts of which hydrolysis to the primary amines was unsatisfactory. Therefore, phthalimide–potassium was used to introduce the amino function. Thus, the reaction products **19** and **20** were easily obtained, purified by recrystallization and characterized by spectroscopic methods. Surprisingly, the cleavage of the ether groups was possible, in contrast with the experience with the ketones **9** and **10**. The catechols **23**, **24** obtained show the IR absorptions required for the functional groups present in the molecule and the expected peaks in the ^{1}H and ^{13}C NMR spectra.

Hydrazinolysis of the phthalimido compounds *yields the* noradrenalones **25** and **26**. This reaction was also possible with the ketones **19** and **20**, resulting in the corresponding veratroles **21** and **22**. The problem with this reaction is the separation of the phthalhydrazide. By treatment with hydrogen iodide, **21** may be converted into **25** in yields of about 24%. The structures given are confirmed by ^{1}H, ^{13}C and ^{19}F NMR investigations. Reduction with hydrogen using a platinum catalyst under normal conditions led to the noradrenalines **27** and **28**. These compounds are described by Kirk,[13] but the synthetic route differs significantly from the strategy used in this paper. The main difference is the introduction of the fluorine atom by Balz–Schiemann reaction into an appropriate veratrole, and the cleavage of the methyl ethers, still a problematic reaction, as the final step of their synthesis. The authors investigated the fluorinated noradrenalines predominantly with respect to their receptor interactions. We, on the other hand, are interested in the stereochemical and chemical properties of these catecholamines. Furthermore, a system consisting of catechols and quinones is a potential electron carrier and therefore we investigated the monovalent oxidation and the associated chemical processes.

In the literature,[13] the proton resonance spectra are mentioned only as far as the absorptions of the aromatic protons are concerned. For this reason, we analysed the total spectrum. The assignment to the OH and NH protons was easily made by hydrogen deuterium exchange. The shifts of the aromatic protons correspond to the numbers already given. The proton of the α-C-atom has a doublet of doublets pattern near $\delta = 5.0$, and the hydrogens of the methylene give a complex multiplet consisting of eight lines near $\delta = 3.0$ (Fig. 1).

The multiplets observed for the protons of the side chain are easily understood in terms of the inequivalence of the methylene protons owing to their diastereotopy. The coupling between the geminal protons is 12.8 Hz for noradrenaline **27** whereas the couplings with the vicinal methine proton were determined to be 9.6 and 3.4 Hz.

The hitherto unknown ^{13}C NMR spectra can be interpreted straightforwardly with the help of the fluorine couplings, the additivity relationship and comparison with the other compounds described in this paper. The ^{19}F NMR spectra confirm the assignment of the H–F couplings used for the interpretation of the ^{1}H spectra.

The synthesis of the difluorocatechols[14] **a** and **b** could be

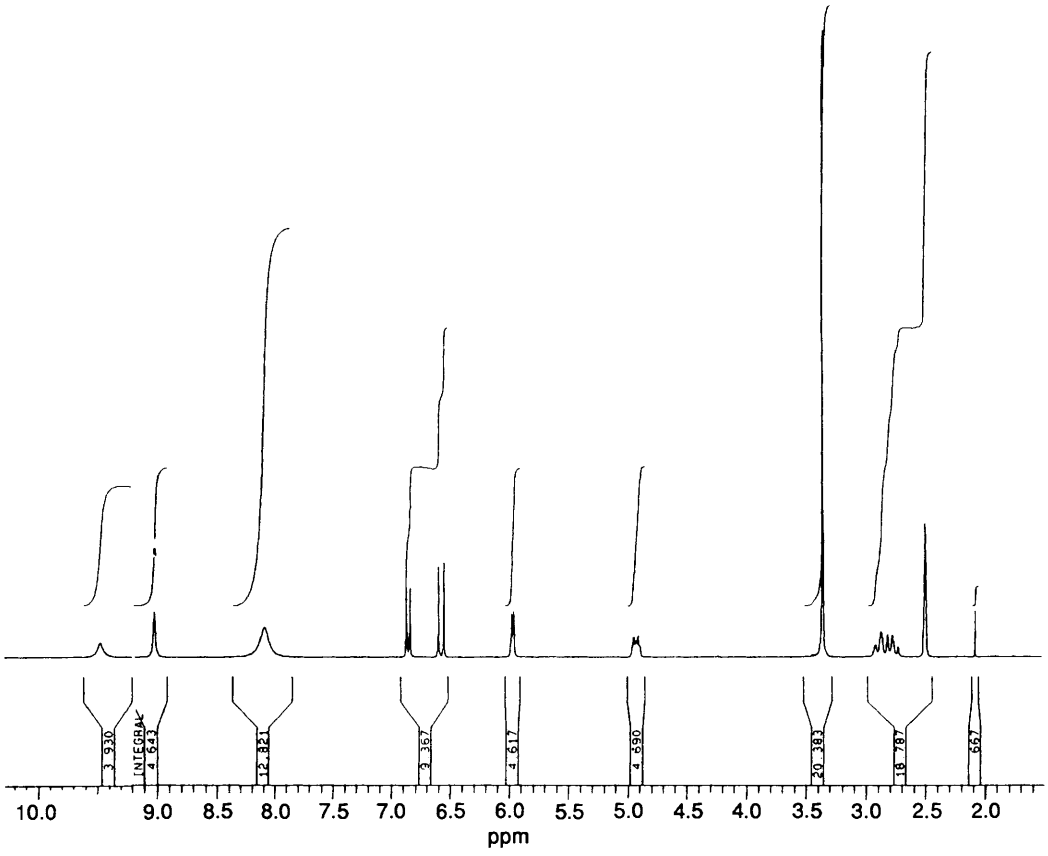
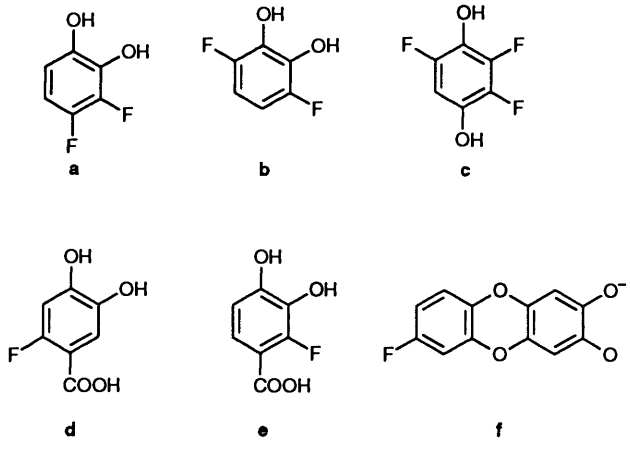


Fig. 1 ^{1}H NMR spectrum of **27** in $(CD_3)_2SO$, room temp., 250 MHz



achieved by starting with the corresponding difluoroanisoles and using the procedure described for the compound **4**. The hydroquinone **c** could be synthesized by nucleophilic substitution of 1,2,3,5-tetrafluorobenzene[15] in position 1 or 3 and subsequent introduction of the second hydroxy group in the position *para* to the methoxy function followed by the cleavage of the ether by treatment with BBr_3[12] in analogy to the catechol **6**. The fluoroveratric acids **d** and **e**[16] were obtained by solvolysis of the bromoacetophenones **17** and **18** as well as demethylation with borontribromide.[14]

EPR and ENDOR Spectroscopy and Reactivity under Oxidative Conditions.—Solutions of the fluorinated catechols in organic solvents, in the presence of appropriate cations or cation precursors undergo autoxidation forming the corresponding semiquinones or semiquinone metal complexes.[17] Thus, the redox properties are not drastically changed by introduction of the fluorine compared with the naturally occurring compounds.[14,18] Both radical types show pronounced dependence of the coupling constants on metal atom and temperature. The EPR data obtained are collected in Table 1 for the 5-fluoro compounds whereas the values obtained for 3-fluoro radicals are given in Table 2. Positions 7 and 8 refer to proton coupling constants of the side chain.

As far as we know there is only one literature citation in which fluorinated *o*-benzosemiquinones are characterized by EPR spectroscopy.[19] The authors reported three different halogen-substituted 3,6-di-*tert*-butylbenzosemiquinones. These radicals have proton coupling constants of approximately 3.5 G and fluorine splittings between 8 and 11 G, depending on the substituent pattern and the counterion used. These results are consistent with our assignment (Table 1). The radicals are indicated by an asterisk next to the number of the corresponding catechol.

The spin-transfer mechanism, the spin-density distribution and the nuclear relaxation of the fluorine nucleus in different fluorine-containing radicals are comprehensively discussed in the literature.[20] In general, the spectroscopic results obtained with other radical types are valid for the semiquinones too, as can be seen from the data observed for the simply substituted radicals **5***, **6***, **a*** and **b***. The positions with high spin density show large fluorine coupling constants with significant linewidth effects (Fig. 2).

The hyperfine structure given in Fig. 2 represents the spectra of two different paramagnetic species. The doublet with larger intensity and smaller *g*-factor (g = 2.0033) can be attributed to a benzodioxine semiquinone **f** formed by formal condensation of two catechols.[21] The other lines are due to the semiquinone complex of **5***. Its hyperfine structure can be observed exclusively immediately after preparation of the sample. With increasing time or temperature, the primary spectrum diminishes in favour of the dioxine radical **f**. This

Table 1 EPR and ENDOR data of the semiquinones derived from 5-fluoropyrocatechol (splitting constants in G)

	Cation	Solvent	a_{Tl}	a_3	a_4	a_5	a_6	a_7	$g = 2.00$
5*	Mes_2Tl	MTHF	21.83		3.61	10.51	1.52[a]		357
5*	Mes_2Tl	Pyr	20.63		3.60	10.45	1.56[a]		
5*	Mes_2Tl	Tol	21.69		3.69	10.65	1.45[a]		
5*	$(C_6H_5)_2Tl$	Pyr	10.32		3.58	10.32	1.66[a]		
5*	$(C_6H_5)_3Sn$	Tol		0.55[b]	3.46	13.22	1.64[b]		423
a*	Mes_2Tl	MTHF	19.96	1.38[c]	3.40[c]	10.38	1.47[c]		366
d*	Mes_2Tl	MTHF	22.18	2.03[d]		9.92			
d*	Mes_2Tl	Pyr	20.36	1.99[d]	0.50[d]	9.75			401
13*	Mes_2Tl	MTHF	21.16			10.13	0.91	3.34	346
23*	Mes_2Tl	MTHF	20.92	2.84[e]		8.36		0.36	434
27*	Mes_2Tl	Pyr	20.66			9.72	1.41[f]	3.34	

[a] Alternative assignment to posn. 3 possible. [b] Alternative assignment possible. [c] ENDOR 233 K. [d] Assignment in analogy to 4-carboxy-*o*-benzosemiquinone. [e] Assignment in analogy to adrenalone semiquinone. [f] Assignment in analogy to noradrenaline semiquinone hydrochloride. [g] ENDOR 273 K. [h] For assignment see ref. 14. [i] Alternative assignment to posn. 6 possible. [k] ENDOR 253 K. [l] Signs were determined by TRIPLE-resonance referring to *o*-benzosemiquinone.[24] [m] ENDOR 233 K. [n] Data from spectra simulation. [o] Splitting constant of $a_8 = 0.17$ G. [p] Splitting constant of $a_8 = 0.16$ G. [q] Pyridine–triethylamine = 3:1.

Table 2 EPR and ENDOR data of the semiquinones derived from 3-fluoropyrocatechol (splitting constants in G)

	Cation	Solvent	a_{Tl}	a_3	a_4	a_5	a_6	a_7	$g = 2.00$
6*[g]	Mes_2Tl	MTHF	21.40	0.53	3.57[h]	3.10[h]			343
6*	Mes_2Tl	Pyr	20.00	0.45[i]	3.50[h]	3.10[h]			345
6*	$(C_6H_5)_2Tl$	Pyr	8.76	0.58[h]	3.66[h]	3.05[h]	0.29[h]		346
6*	Mes_2Tl	Pyr	19.40	0.59[b]	4.00[h]	3.00[h]	0.46[b]		
6*	$(C_6H_5)_3Sn$	Tol		0.31[k]	4.80[h,k]	2.40[h,k]	1.56		
6*[k,l]	K	Eth		−0.58	−3.59[h]	−2.91[h]	+0.71		458
b*	Mes_2Tl	MTHF	18.99	0.59	3.06	3.06[m]	0.59[m]		360
b*	Mes_2Tl	Pyr	16.59	0.48	3.32	3.32	0.48		360
b*[l]	K	Eth		+0.11	−2.99	−2.99[g]	+0.11[g]		
e*	Mes_2Tl	MTHF	21.87	2.03[d]		3.44[d]			
e*	Mes_2Tl	Pyr	19.75	1.75[d]	0.28 (a_{Tl})	3.39[d]	0.28		387
14*[n]	Mes_2Tl	MTHF	20.79	0.95[k]		3.61	0.61	2.57[o]	336
14*	Ph_2Tl	Pyr	8.69	0.73[b]		3.61	0.70[b]	2.58[p]	
24*	Mes_2Tl	MTHF	19.46	2.94[g]		2.88[g]	0.20		422
28*	Mes_2Tl	*q*	19.74	0.62[k]		3.71[b,k]	0.58[k]	2.30[b,k]	

Footnotes as Table 1.

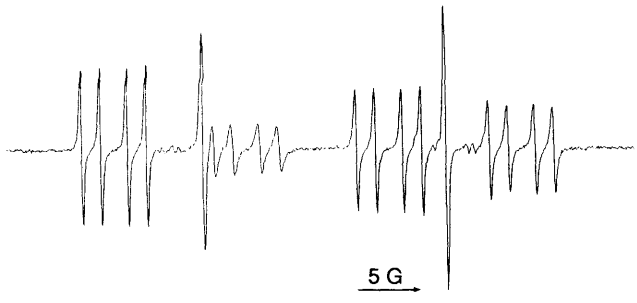


Fig. 2 EPR spectrum of **5*** Mes_2Tl in MTHF at 293 K 3 h after preparation

species is a common reaction product of *o*-benzosemiquinones if they are generated in aprotic solvents, but the rate of formation is significantly accelerated by the fluoro substituent. Therefore, we assume that the rate-determining step is an initial nucleophilic substitution of the fluorine by an oxygen forming a diphenyl ether. This reaction obviously occurs after oxidation either in the semiquinone or in the quinone redox state and is a typical reaction product observed with all radicals derived from compound **5** listed in Table 1.

The unusual intensity ratio in the high-field doublet is 5:1 for **5*** with dimesitylthallium as the counterion in pyridine at room temperature due to anisotropic contributions already mentioned. With increasing temperature, this ratio decreases continuously and at 353 K it reaches 2:1; at higher temperature the radical decomposes. In the organothallium complexes the smallest coupling due to any position *ortho* to the oxygens cannot be resolved; this splitting can, however, be detected in the tin complex. ENDOR and TRIPLE resonance experiments were not successful with **5*** under all conditions applied, however, with the 3-fluorosemiquinone **6*** multiresonance experiments could be carried out, giving rise to the relative signs given in Table 2.

The hyperfine structure of radical **6*** does not change over several days (the dioxine formation, in particular, was not observed) and therefore the interpretation of the secondary radical derived from **5*** is confirmed by this result.

The 3,4-difluoropyrocatechol **a** can be oxidized in the presence of dimesitylthallium hydroxide in MTHF by air. The behaviour of **a*** is a combination of the properties of **5*** and **6***. Owing to anisotropic contributions, the intensity ratio of the large F-doublet splitting is about 2.5:1. The formation of the benzodioxine radical **f** starts about 3 h after generation and therefore the condensation reaction is slow compared with **5***. ENDOR spectra with a poor signal-to-noise ratio were obtained which allowed the assignment of the two small splittings listed in Table 1.

The semiquinone of **b** shows a triplet of triplet hyperfine structure in accordance with its symmetry. The signal-to-noise ratio and the relaxation properties permit multiresonance experiments. The relative signs of the fluorine coupling constants observed are the opposite of the corresponding proton splittings.

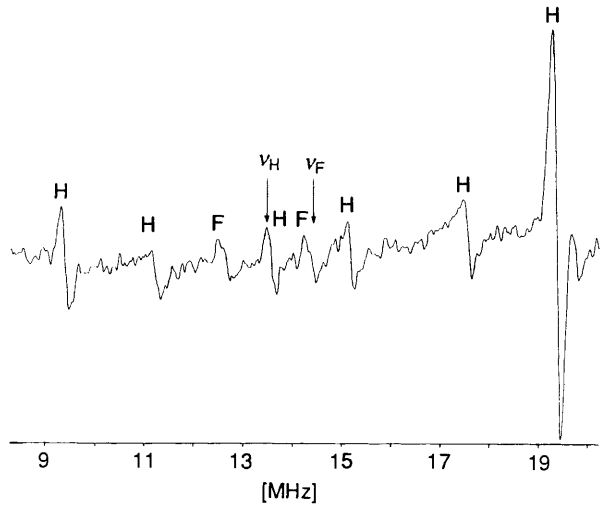


Fig. 3 ENDOR spectrum of **28*** in pyridine–triethylamine at 253 K

The spin density distribution of the acids **d*** and **e*** are dominated by the carboxy function as can be shown by comparison with the 4-carboxy-*o*-benzosemiquinone.[18] In the case of **e*** in pyridine, a second small thallium coupling is observed indicating the formation of a thallium salt of the carboxy group.

The ethyl-substituted fluoropyrocatechols **13**, **14** can be easily oxidized in the presence of organothallium compounds resulting in the semiquinones. **14*** is a persistent radical whereas **13*** easily undergoes nucleophilic substitution leading to the benzodioxine radical **f** already mentioned. The assignment of the splittings observed is straightforward. With radical **13*** in MTHF, ENDOR experiments were possible, and therefore the coupling of 0.95 G could be unambiguously attributed to the fluorine nucleus.

The catechols **23** and **24** are derivatives of adrenalone and therefore their oxidation requires strong oxidation agents[22] such as PbO_2 or AgO. The EPR spectrum of **24*** shows a doublet of triplets indicating a similar coupling of the electron with the proton in position 5 and the fluorine nucleus. Obviously, the combination of acyl and fluorine substitution leads to a significant redistribution of the spin density; a similar, but less significant effect is observed with the radical **e***. The assignment of the coupling constants given in Table 2 was achieved by ENDOR spectroscopy.

Semiquinone **23*** shows a relatively large coupling constant for position 3 indicating a particular spin-density distribution in the adrenalone-related radicals corresponding to those of the similarly substituted radical **d***. The differences in the electronic properties influence the reactivity of **23*** too, as indicated by a very slow formation of the dioxine radical **f**.

The generation of the 3-fluoronoradrenaline radical **28*** with a good signal-to-noise ratio was possible in a mixture consisting of pyridine–triethylamine 3:1 (Fig. 3). The ENDOR spectrum enabled us to distinguish between the fluorine and the small proton coupling. TRIPLE resonance experiments failed, and therefore an unambiguous assignment of the large proton splittings was not possible. However, by comparison with **14*** on the one hand, and **27*** with **13*** on the other, the assignments given in Table 2 seem to be reasonable. Oxidation of **27** in pyridine yields the less persistent 5-fluoronoradrenaline semiquinone **27*** with a poor signal-to-noise ratio and the secondary dioxine radical **f** representative of this type of substitution. After a few minutes the radical **f** dominated the spectrum. The assignment was made by comparison with noradrenaline[17] and the other related radicals listed in Table 1.

Oxidation of **27** and **28** in methanol in the presence of potassium hydroxide led in both cases to the same radical with an extended hyperfine structure. ENDOR and TRIPLE resonance experiments led to an interpretation of the spectra by interaction of the free electron with one set of six (1.02 G) and a second set of two (0.21 G) equivalent protons. This hyperfine structure is due to 4,5-dimethoxybenzosemiquinone-(1,2).[23] This radical indicates that independent of the position of the fluorine atom, both the fluorine and the side chain are substituted by methoxy groups. The reaction in 5 position is clearly the already mentioned nucleophilic substitution of electron withdrawing groups. However, the exchange of the fluorine in position 3 is difficult to explain and may proceed *via* an arene-type transition state.

Experimental

Melting points were determined with a Büchi apparatus (Dr. Tottoli). Elemental analyses were obtained from the Microanalytical Laboratory, *Chemisches Institut der Universität Tübingen* (W. Bock and H. Wurmstich). 250 MHz ^1H and 62.9 MHz ^{13}C NMR spectra were run on a Bruker AC 250 instrument, 400 MHz ^1H and 100.6 MHz ^{13}C NMR spectra on a Bruker WM 400 and 188.3 MHz ^{19}F NMR spectra on a Bruker MSL 200. IR (KBr or film) spectra were run on a Perkin-Elmer IR 281 B, 700 B spectrophotometer. Mass spectra (70 eV) were run on a Varian MAT-711 A, Finnigan/MAT TSQ-70 spectrometer. EPR spectra were taken on a Bruker ESP 300 and ENDOR spectra on a Varian E-Line-Century EPR spectrometer equipped with a Bruker ER 810 ENDOR unit (500 W amplifier) and a Bruker ER 140 data system.

EPR Measurements.—A sample of the pyrocatechol and the appropriate cation precursor were placed in the EPR tube and dissolved in an appropriate solvent. The brenzcatechine was oxidized with air or in some cases with a small amount of lead dioxide. The probe was flushed with nitrogen for 5–10 min in order to remove the oxygen from the solvent.

4-Fluoropyrocatechol **5** was prepared according to a well known method:[4] ν_{max}/cm^{-1} **3**: 3450br (OH), 3080 (ArH), 1650 (C=O) and 1620 (C=C); **5**: 3300–3400 (OH) and 1630, 1520 (C=C); *m/z* **3**: 154 (62%, M^+), 139 (100), 112 (29) and 111 (29); **5**: 128 (100%, M^+), 110 (35) and 82 (49); $\delta_H([^2H_6]DMSO)$ **3**: 11.60 (s, 1 H, OH), 7.66 (dd, J = 9.4, 3.2 Hz, 1 H, H3), 7.40 (ddd, J = 9.1, 8.1, 3.2 Hz, 1 H, H5), 6.98 (dd, J = 9.1, 4.6 Hz, 1 H, H6) and 2.63 (s, 3 H, CH_3); **5**: 9.08br (OH), 6.67 (dd, J = 8.8, 6.0 Hz, 1 H, H6), 6.53 (dd, J = 10.1, 3.0 Hz, 1 H, H3) and 6.39 (td, J = 8.6, 3.1 Hz, 1 H, H5); $\delta_C([^2H_6]DMSO)$ **3**: 203.1 (d, J = 1.8 Hz, C=O), 156.8 (s, C-1), 154.5 (d, J = 235.7 Hz, C-4), 123.2 (d, J = 23.6 Hz, C-5), 120.6 (d, J = 6.3 Hz, C-2[a]), 119.1 (d, J = 7.6 Hz, C-6[a]), 116.1 (d, J = 23.3 Hz, C-3) and 28.0 (s, CH_3); **5**: 155.5 (d, J = 233.5 Hz, C-4), 146.2 (d, J = 11.4 Hz, C-2), 141.7 (d, J = 2.4 Hz, C-1), 115.5 (d, J = 10.1 Hz, C-6), 104.6 (d, J = 22.1 Hz, C-5[a]), 103.0 (d, J = 25.4 Hz, C-3[a]) ([a] assignment exchangeable).

The guaiacol **4** was synthesized according to the literature[5] and demethylated in analogy to a well known method:[12] ν_{max}/cm^{-1} 3500–3300br (OH), 1620, 1510 (C=C) and 1230 (C–F); *m/z* 128 (100%, M^+), 108 (11), 52 (24) and 51 (17); $\delta_H([^2H_6]DMSO)$ 9.17 (br, OH) and 6.66–6.53 (m); $\delta_C([^2H_6]DMSO)$ 152.2 (d, J = 237.6 Hz, C-3), 147.7 (d, J = 5.7 Hz, C-1), 133.3 (d, J = 14.2 Hz, C-2), 118.4 (d, J = 9.4 Hz, C-5), 111.7 (d, J = 1.6 Hz, C-6) and 106.5 (d, J = 18.9 Hz, C-4).

The veratroles **7** and **8** were prepared by methylation of **5** and **4**:[5] $\delta_H(CDCl_3$; 400 MHz) **7**: 6.76 (dd, J = 8.9, 5.4 Hz, 1 H, H6), 6.63 (dd, J = 10.0, 2.9 Hz, 1 H, H3), 6.58 (dt, J = 8.7, 2.9 Hz, 1 H, H5), 3.86 (s, 3 H, OCH_3) and 3.85 (s, 3 H, OCH_3); **8**: 6.98–6.89 (m, 1 H, H5), 6.74–6.66 (m, 2 H, H4, H6), 3.91 (d, J = 0.8 Hz, 3 H, OCH_3) and 3.85 (s, 3 H, OCH_3); $\delta_C(CDCl_3)$ **7**:

157.3 (d, J = 238.4 Hz, C-4), 149.8 (d, J = 9.9 Hz, C-2), 145.3 (d, J = 2.7 Hz, C-1), 111.6 (d, J = 9.8 Hz, C-6), 105.6 (d, J = 22.6 Hz, C-5), 100.0 (d, J = 27.5 Hz, C-3), 56.2 (s, OCH_3) and 55.8 (s, OCH_3); **8**: 156.2 (d, J = 245.0 Hz, C-3), 153.1 (d, J = 5.0 Hz, C-1), 137.3 (d, J = 13.1 Hz, C-2), 123.2 (d, J = 9.7 Hz, C-5), 108.9 (d, J = 19.8 Hz, C-4), 107.8 (s, C-6), 61.3 (d, J = 3.1 Hz, OCH_3) and 56.1 (s, OCH_3).

General Method for the Preparation of **9**, **10**.—A suspension of $AlCl_3$ (2.8 g, 21.3 mmol) in dry $(CH_2)_2Cl_2$ was cooled to −20 °C and then acetyl chloride (1.85 cm^3; 25.5 mmol) was added dropwise and subsequently the veratrole **7** or **8** (2.7 g, 17 mmol) dissolved in 10 cm^3 $(CH_2)_2Cl_2$ was added dropwise to the solution. This solution was stirred for 30 min at −20 °C, then the mixture was allowed to warm with continuous stirring for 2 h. The mixture was poured onto ice and the layers were separated. The aqueous solution was extracted twice with ether; the ether extracts were combined, washed with H_2O, dried with $MgSO_4$ and concentrated. After evaporation the crude products **9** and **10** were recrystallized from light petroleum (b.p. 60–90 °C) to yield 2.85 g (84.5%) and 2.75 g (81.8%) of colourless crystals, respectively. M.p. 100–101 °C (**9**), m.p. 55 °C (**10**); **9**: ν_{max}/cm^{-1} 3080, 3000 cm^{-1} (ArH), 3000, 2980, 2940 (aliphatic CH), 2820 (OC–H), 1665 (C=O) and 1610, 1515 (C=C); **10**: 3020, 3000 (ArH), 2960, 2940 (aliphatic CH), 2850 (OC–H), 1660 (C=O) and 1610, 1570, 1510 (C=C); m/z **9**: 198 (38%, M^+), 183 (100), 184 (30), 169 (49), 140 (15) and 43 (30); **10**: 198 (43%, M^+), 183 (100), 155 (8), 140 (9) and 43 (21); $\delta_H(CDCl_3)$ **9**: 7.40 (d, J = 6.8 Hz, 1 H, H2), 6.62 (d, J = 12.2 Hz, 1 H, H5), 3.93 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3) and 2.61 (d, J = 5.7 Hz, 3 H, CH_3); **10**: 7.61 (dd, J = 9.0, 8.1 Hz, 1 H, H6), 6.73 (dd, J = 9.0, 1.5 Hz, 1 H, H5), 3.91 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3) and 2.57 (d, J = 5.2 Hz, 3 H, CH_3); $\delta_C(CDCl_3)$ **9**: δ = 194.4 (d, J = 4.1 Hz, CO), 158.3 (d, J = 250.5 Hz, C-6), 154.3 (d, J = 10.6 Hz, C-4), 145.5 (s, C-3), 116.9 (d, J = 14.0 Hz, C-1), 110.7 (d, J = 4.2 Hz, C-2), 99.9 (d, J = 30.6 Hz, C-5), 56.5 (s, OCH_3), 56.3 (s, OCH_3) and 31.4 (d, J = 8.6 Hz, CH_3); **10**: 194.6 (d, J = 3.3 Hz, CO), 157.8 (d, J = 5.4 Hz, C-4), 156.7 (d, J = 254.5 Hz, C-2), 137.0 (d, J = 14.9 Hz, C-3), 125.2 (d, J = 3.7 Hz, C-6), 119.8 (d, J = 12.1 Hz, C-1), 107.2 (d, J = 2.2 Hz, C-5), 61.6 (d, J = 3.1 Hz, OCH_3), 56.3 (s, OCH_3) and 31.2 (d, J = 7.5 Hz, CH_3) [Found: **9**: C, 60.7; H, 5.7; **10**: C, 60.75; H, 5.7. Calc. for $C_{10}H_{11}FO_3$ (M = 198.19): C, 60.61; H, 5.60%].

General Method for the Preparation of **11**, **12**.—**9** or **10** (1 g, 5 mmol) in acetic acid (25 cm^3) were hydrogenated at room temperature using Pd–C. The catalyst was filtered off and the solution concentrated. The residue was dissolved in CH_2Cl_2 and washed with water, aqueous sodium hydrogen carbonate and once more with water. The organic layer was dried with $CaCl_2$ and evaporated to yield 0.83 g (90.6%) and 0.79 g (86%) of colourless oils. The boiling points were not determined.

ν_{max}/cm^{-1} **11**: 2970, 2940 (aliphatic CH), 2860, 2840 (OC–H), 1630, 1515 (C=C) and 1110 (C–F); **12**: 2970, 2940, 2880 (aliphatic CH), 2840 (OC–H), 1620, 1505 (C=C) and 1100 (C–F); m/z **11**: = 184 (51%, M^+) and 169 (100); **12**: 184 (58%, M^+) and 169 (100); $\delta_H(CDCl_3)$ **11**: 6.70 (d, J = 7.2 Hz, 1 H, H2), 6.60 (d, J = 11.1 Hz, 1 H, H5), 3.85 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 2.60 (q, J = 7.6 Hz, 2 H, CH_2) and 1.20 (t, J = 7.6 Hz, 3 H, CH_3); **12**: 6.82 (dd, J = 8.6, 8.1 Hz, 1 H, H6), 6.61 (dd, J = 8.6, 1.7 Hz, 1 H, H5), 3.91 (d, J = 0.8 Hz, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 2.60 (qd, J = 7.6, 0.8 Hz, 2 H, CH_2) and 1.20 (t, J = 7.6 Hz, 3 H, CH_3); $\delta_C(CDCl_3)$ **11**: 154.6 (d, J = 237.4 Hz, C-6), 147.2 (d, J = 9.7 Hz, C-4), 144.9 (d, J = 2.2 Hz, C-3), 121.3 (d, J = 17.4 Hz, C-1), 112.2 (d, J = 6.5 Hz, C-2), 99.9 (d, J = 28.7 Hz, C-5), 56.3 (s, OCH_3), 56.0 (s, OCH_3), 21.7 (d, J = 1.6 Hz, CH_2) and 14.7 (s, CH_3); **12**: 154.5 (d, J = 244.6 Hz, C-2), 151.7 (d, J = 4.8 Hz, C-4), 137.2 (d, J = 14.0 Hz, C-3), 124.6 (d, J = 15.2 Hz, C-1), 122.8 (d, J = 6.7 Hz, C-6), 107.2 (d, J = 3.1 Hz, C-5), 61.4 (d, J = 3.6 Hz, OCH_3), 56.2 (s, OCH_3), 21.8 (d, J = 2.8 Hz, CH_2) and 14.6 (s, CH_3) [Found: **11**, C, 65.05; H, 7.0; **12**, C, 64.9; H, 6.9. Calc. for $C_{10}H_{13}FO_2$ (M = 184.21): C, 65.20; H, 7.11%].

General Method for the Preparation of **13**, **14**.—**11** or **12** (0.6 g, 3.3 mmol) in dry CH_2Cl_2 (15 cm^3) were cooled to −70 °C in a dry ice–acetone bath under a nitrogen atmosphere and then BBr_3 (7.3 cm^3; 6.6 mmol; 1.0 mol dm^{-3} solution in CH_2Cl_2) was added. These solutions were stirred for 2 h at room temperature. The reaction mixture was cooled to 0 °C, hydrolysed and the layers separated. The aqueous layer was extracted twice with ether, the ether layers were combined, washed with aqueous sodium hydrogen carbonate and water, dried with $MgSO_4$ and concentrated. The oily residue crystallized after treatment with light petroleum (b.p. 30–50 °C). Recrystallization of **13** from hexane yielded 0.45 g (87.4%) and **14** from light petroleum (b.p. 60–90 °C) 0.46 g (88.5%). M.p. **13** 77–78 °C; m.p. **14** 57 °C. ν_{max}/cm^{-1} **13**: 3460–3300 (OH), 2980, 2940, 2880 (aliphatic CH), 1640, 1525, 1510 (C=C) and 1100 (C–F); **14**: 3450–3250 (OH), 2970, 2930, 2880 (aliphatic CH), 1630, 1610, 1515 (C=C) and 1090 (C–F); m/z **13**: 156 (37%, M^+) and 141 (100); **14**: = 156 (32%, M^+) and 141 (100); $\delta_H(CDCl_3)$ **13**: 6.68 (d, J = 7.2 Hz, 1 H, H2), 6.60 (d, J = 10.2 Hz, 1 H, H5), 5.26 (br, OH), 4.93 (br, OH), 2.55 (q, J = 7.6 Hz, 2 H, CH_2) and 1.17 (t, J = 7.6 Hz, 3 H, CH_3); **14**: 6.63 (m, 2 H, H5, H6), 5.20 (br, OH), 2.60 (qd, J = 7.6, 1.2 Hz, 2 H, CH_2) and 1.20 (t, J = 7.6 Hz, 3 H, CH_3); $\delta_C(CDCl_3)$ **13**: 154.8 (d, J = 237.6 Hz, C-6), 142.0 (d, J = 11.8 Hz, C-4), 139.1 (d, not resolved, C-3), 122.7 (d, J = 18.4 Hz, C-1), 115.8 (d, J = 6.5 Hz, C-2), 103.2 (d, J = 27.5 Hz, C-5), 21.5 (d, J = 2.0 Hz, CH_2) and 14.6 (s, CH_3); **14**: 149.6 (d, J = 236.4 Hz, C-2), 143.2 (d, J = 3.8 Hz, C-4), 131.2 (d, J = 16.9 Hz, C-3), 123.2 (d, J = 14.2 Hz, C-1), 119.8 (d, J = 6.2 Hz, C-6), 110.5 (d, J = 3.1 Hz, C-5), 21.7 (d, J = 2.0 Hz, CH_2) and 14.6 (s, CH_3); $\delta_F(CDCl_3$; internal C_6F_6) **13**: −125.28 (ddt, J = 10.2, 7.2, 1.1 Hz) [Found: **13**, C, 61.85; H, 5.85; **14**, C, 61.9; H, 5.9. Calc. for $C_8H_9FO_2$ (M = 156.16): C, 61.53; H, 5.81%].

General Method for the Preparation of **15**, **16**.—At −40 °C $NaBH_4$ (3.84 g, 0.1 mol) was added slowly to 250 cm^3 absolute methanol. **9** or **10** (2 g, 0.01 mol) in absolute methanol was then added dropwise. The reaction mixtures were stirred at −40 °C until the H_2 evolution was complete. The methanol was evaporated off and the residue was dissolved in H_2O and acidified with concentrated HCl to pH 7–8. The resultant solutions were extracted with ether and the combined ether layers washed with H_2O and dried over $MgSO_4$. After evaporation the oily residue of **15** was crystallized after treatment with light petroleum (b.p. 30–50 °C) and further recrystallized from toluene yielding 1.80 g (90%), m.p. 56–57 °C. The residue of **16** could not be crystallized, therefore it was chromatographed on silica gel with toluene to yield 1.64 (82%) of a colourless oil, the boiling point of which was not determined. ν_{max}/cm^{-1} **15**: 3290 (OH), 2980, 2970, 2920 (aliphatic CH), 2840, 2820 (OC–H) and 1635, 1510 (C=C); **16**: 3500–3300 (OH), 2970, 2940 (aliphatic CH), 2940 (OC–H) and 1620, 1500 (C=C); m/z **15**: 200 (67%, M^+), 185 (100), 157 (53), 142 (25), 126 (20), 43 (26); **16**: = 200 (54) [M^+], 185 (100) and 157 (28); $\delta_H(CDCl_3)$ **15**: 6.97 (d, J = 7.0 Hz, 1 H, H2), 6.59 (d, J = 11.5 Hz, 1 H, H5), 3.88 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 5.17 (q, J = 6.4 Hz, 1 H, CH) and 1.49 (d, J = 6.4 Hz, 3 H, CH_3); **16**: 7.08 (t, J = 8.4 Hz, 1 H, H6), 6.65 (dd, J = 8.7, 1.7 Hz, 1 H, H5), 3.88 (d, J = 0.7 Hz, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 5.08 (q, J = 6.6 Hz, 1 H, CH) and 1.45 (d, J = 6.6 Hz, 3 H, CH_3); $\delta_C(CDCl_3)$ **15**: 153.4 (d, J = 237.9 Hz, C-6), 148.7 (d, J = 10.1 Hz, C-4), 145.3 (d, J = 2.3 Hz, C-3), 123.3 (d, J = 14.9

Hz, C-1), 108.8 (d, J = 6.1 Hz, C-2), 99.9 (d, J = 28.3 Hz, C-5), 63.9 (d, J = 1.8 Hz, CH), 56.4 (s, OCH_3), 56.1 (s, OCH_3) and 24.2 (s, CH_3); **16**: 153.6 (d, J = 5.6 Hz, C-4), 153.3 (d, J = 245.2 Hz, C-2), 136.9 (d, J = 13.6 Hz, C-3), 126.5 (d, J = 12.6 Hz, C-1), 120.1 (d, J = 6.2 Hz, C-6), 106.4 (s, C-5), 64.0 (d, J = 2.9 Hz, CH), 61.4 (d, J = 3.1 Hz, OCH_3), 56.3 (s, OCH_3) and 24.0 (s, CH_3) [Found: **15**, C, 60.5; H, 5.9; **16**, C, 59.85; H, 6.7. Calc. for $C_{10}H_{13}FO_3$ (M = 200.21): C, 59.99; H, 6.54%].

General Method for the Preparation of **17**, **18**.—Bromine (4.8 g, 0.03 mol) in abs. $CHCl_3$ (20 cm^3) was slowly dropped to a solution of **9** or **10** (6 g, 0.03 mol) in 50 cm^3 abs. $CHCl_3$. The resultant solutions were stirred for 2 h at room temperature and then the reaction mixtures neutralized with 10% aqueous sodium hydroxide. The layers were separated and the organic solution washed twice with H_2O and dried with $MgSO_4$. After removal of the solvent the crude material of **17** and **18** was recrystallized from ethyl acetate–cyclohexane to yield 7.40 g (89%) and 5.15 g (62%) of white needles, respectively. M.p.s were 125 °C (**17**) and 90 °C (**18**). ν_{max}/cm^{-1} **17**: 3100/3080 (ArH), 2980, 2960, 2940 (aliphatic CH), 2840 (OC–H), 1690 (C=O) and 1605, 1510 (C=C); **18**: 3020, 3000 (ArH), 2950 (aliphatic CH), 2840 (OC–H), 1690 (C=O) and 1605, 1570, 1505 (C=C); m/z **17**: 278, 276 (12%, M^+), 183 (100) and 140 (7); **18**: 278, 276 (7%, M^+), 198 (12), 183 (100) and 43 (14); $\delta_H(CDCl_3)$ **17**: 7.40 (d, J = 6.8 Hz, 1 H, H2), 6.65 (d, J = 12.4 Nz, 1 H, H5), 4.49 (d, J = 2.7 Hz, 2 H, CH_2), 3.95 (s, 3 H, OCH_3) and 3.90 (s, 3 H, OCH_3); **18**: 7.70 (dd, J = 9.0, 7.9 Hz, 1 H, H6), 6.82 (dd, J = 9.0, 1.5 Hz, 1 H, H5), 4.49 (d, J = 2.6 Hz, 2 H, CH_2), 3.96 (s, 3 H, OCH_3) and 3.93 (s, 3 H, OCH_3); $\delta_C(CDCl_3)$ **17**: 187.5 (d, J = 5.0 Hz, CO), 157.8 (d, J = 250.4 Hz, C-6), 155.1 (d, J = 10.6 Hz, C-4), 145.9 (s, C-3), 113.7 (d, J = 14.1 Hz, C-1), 111.1 (d, J = 4.2 Hz, C-2), 99.7 (d, J = 30.6 Hz, C-5), 56.5 (s, OCH_3), 56.3 (s, OCH_3) and 35.9 (d, J = 11.3 Hz, CH_2); **18**, 187.5 (d, J = 3.9 Hz, CO), 158.7 (d, J = 5.7 Hz, C-4), 156.1 (d, J = 253.8 Hz, C-2), 137.0 (d, J = 14.6 Hz, C-3), 126.1 (d, J = 3.8 Hz, C-6), 116.6 (d, J = 12.1 Hz, C-1), 107.9 (d, J = 2.0 Hz, C-5), 61.6 (d, J = 2.8 Hz, OCH_3), 56.5 (s, OCH_3), 36.0 (d, J = 9.9 Hz, CH_2) [Found: **17**, C, 43.35; H, 3.75; Br, 29.08; **18**, C, 43.65; H, 3.75; Br, 28.49. Calc. for $C_{10}H_{10}BrFO_3$ (M = 276, 278): C, 43.35; H, 3.64; Br, 28.84%].

6-Fluoro-3,4-dimethoxy-ω-phthalimidoacetophenone **19**.—**17** (2 g, 7.2 mmol) was dissolved in 35 cm^3 DMF and potassium phthalimide (1.4 g, 7.2 mmol) was added. The temperature was raised to about 10 °C and after 5 min precipitation was observed. Regardless of this the reaction mixture was stirred for 4 h at 50–60 °C and the fine, yellow precipitate was filtered off by suction and washed with cold water until the yellowish colour disappeared. After evaporation of the solvent, recrystallization of the residue from toluene yielded 2.15 g (87%) of colourless crystals, m.p. 224–225 °C. ν_{max}/cm^{-1} 3040 (ArH), 2980, 2940 (aliphatic CH), 2860, 2825 (OC–H), 1775, 1725 (Imid-C=O), 1685 (C=O) and 1610, 1520 (C=C); m/z 343 (6%, M^+), 183 (100) and 77 (6); $\delta_H(CDCl_3)$ 7.93–7.74 (m, 4 H, ArH), 7.41 (d, J = 6.5 Hz, 1 H, H2), 6.70 (d, J = 12.3 Hz, 1 H, H5), 5.03 (d, J = 4.4 Hz, 2 H, CH_2), 3.97 (s, 3 H, OCH_3) and 3.88 (s, 3 H, OCH_3); $\delta_C(CDCl_3)$ 187.9 (d, J = 5.6 Hz, CO), 168.0 (s, CO–N), 158.7 (d, J = 250.4 Hz, C-6), 155.2 (d, J = 10.8 Hz, C-4), 145.8 (s, C-3), 134.1 (s, C-4′, C-5′), 132.2 (s, C-1′, C-2′), 123.5 (s, C-3′, C-6′), 113.9 (d, J = 15.1 Hz, C-1), 110.5 (d, J = 4.9 Hz, C-2), 99.7 (d, J = 30.4 Hz, C-5), 56.5 (s, OCH_3), 56.2 (s, OCH_3) and 47.6 (d, J = 15.0 Hz, CH_2) [Found: C, 63.3; H, 4.30; N, 3.90. Calc. for $C_{18}H_{14}FNO_5$ (M = 343.31): C, 62.97; H, 4.11; N, 4.10%].

2-Fluoro-3,4-dimethoxy-ω-phthalimidoacetophenone **20**.—Potassium phthalimide (1.4 g, 7.2 mmol) was added to a solution of **18** (2 g, 7.2 mmol) in 25 cm^3 DMF. The yellow suspension was stirred for 10 min at room temperature, during which time the colour darkened to orange. After 5 h of stirring at 60–70 °C and cooling to room temperature 25 cm^3 of $CHCl_3$ were added. The reaction mixture was diluted with water, the layers separated and the water extracted twice with $CHCl_3$. The combined organic layers were washed with water and dried with $MgSO_4$. Recrystallization of the residue from ethyl acetate yielded 2.2 g (89.1%) of white needles, m.p. 152–154 °C. ν_{max}/cm^{-1} 2950 (aliphatic CH), 2850 (OC–H), 1775, 1720 (Imid-C=O), 1690 (C=O) and 1600, 1570 (C=C); m/z 343 (4%, M^+), 183 (100), 140 (7), 147 (11) and 76 (13); $\delta_H(CDCl_3)$ 7.92–7.70 (m, 4 H, ArH), 7.73 (dd, J = 9.1, 7.7 Hz, 1 H, H6), 6.81 (dd, J = 9.1, 1.4 Hz, 1 H, H5), 5.02 (d, J = 4.2 Hz, 2 H, CH_2) and 3.96 (s, 6 H, OCH_3); $\delta_C(CDCl_3)$ 188.0 (d, J = 5.3 Hz, CO), 167.9 (s, CO–N), 158.8 (d, J = 5.7 Hz, C-4), 157.0 (d, J = 253.8 Hz, C-2), 137.1 (d, J = 14.5 Hz, C-3), 134.1 (s, C-4′, C-5′), 132.2 (s, C-1′, C-2′), 125.7 (d, J = 4.6 Hz, C-6), 123.5 (s, C-3′, C-6′), 116.8 (d, J = 13.3 Hz, C-1), 107.9 (s, C-5), 61.8 (d, J = 2.8 Hz, OCH_3), 56.5 (s, OCH_3) and 47.5 (d, J = 13.8 Hz, CH_2) [Found: C, 62.45; H, 4.31; N, 3.80. Calc. for $C_{18}H_{14}FNO_5$ (M = 343.31): C, 62.97; H, 4.11; N, 4.10%].

General Method for the Preparation of **21**, **22** *and* **25**, **26**.—85% Hydrazine hydrate solution (0.7 cm^3, 11 mmol) was added to each suspension of **19**, **20** (1.8 g, 5.4 mmol) in ethanol or **23**, **24** in methanol. The ethanol or methanol reaction mixtures were refluxed for 3 h and 30 min, respectively. The mixtures were allowed to cool to room temperature, after which concentrated HCl (9, 6 cm^3, respectively) were added, and the reaction was heated under reflux for about 10 min. After cooling with ice water the precipitated phthalhydrazide was sucked off and washed with cold ethanol and methanol, respectively. After evaporation the crude products obtained were recrystallized: **21** from methanol–ethanol yield 0.96 g (71%), melting range 235–239 °C; **22** from ethanol–ethyl acetate yield 0.82 g (61%), melting range 210–215 °C; **25** from water–methanol yield 0.90 g (66.7%), melting range 237–239 °C and **26** from methanol–ethanol yield 1.03 g (85.7%), melting range 258–260 °C. Because the aminophthalimide moiety was hard to separate, it was necessary to recrystallize the products several times until the aminophthalimide was completely removed. ν_{max}/cm^{-1} **21**: 3450 (NH), 2980 (NH), 1670 (C=O) and 1610, 1580, 1510 (C=C); δ_H **21** (D_2O + TSP*) 7.46 (d, J = 6.6 Hz, 1 H, H2), 6.97 (d, J = 12.9 Hz, 1 H, H5), 4.52 (d, J = 3.6 Hz, 2 H, CH_2), 3.95 (s, 3 H, OCH_3) and 3.89 (s, 3 H, OCH_3); **22** ([$^2H_6$]DMSO) 8.49 (s, 3 H, NH_3), 7.73 (dd, J = 9.1, 1.2 Hz, 1 H, H5) 4.35 (dd, J = 5.6, 3.0 Hz, 2 H, CH_2), 3.94 (s, 3 H, OCH_3) and 3.82 (s, 3 H, OCH_3); δ_C([$^2H_6$]DMSO) **21**: 188.4 (d, J = 4.4 Hz, CO), 158.2 (d, J = 250.3 Hz, C-6), 155.4 (d, J = 11.2 Hz, C-4), 145.5 (s, C-3), 112.9 (d, J = 13.8 Hz, C-1), 109.7 (d, J = 3.8 Hz, C-2), 100.9 (d, J = 29.9 Hz, C-5), 56.7 (s, OCH_3), 56.0 (s, OCH_3) and 47.5 (d, J = 13.2 Hz, CH_2) [Found: **21**, C, 48.6; H, 5.05; N, 5.2; Cl, 13.4; **22**, C, 48.6; H, 4.95; N, 5.2; Cl, 13.4. Calc. for $C_{10}H_{13}ClFNO_3$ (M = 249.67): C, 48.11; H, 5.25; N, 5.60; Cl, 14.20%].

Analytical data of **25**, **26**: ν_{max}/cm^{-1} **25**: 3400 (OH), 3170 (NH), 1690 (C=O) and 1630, 1605, 1510 (aromatic C=C); **26**: 3300–3200 (OH), 3100–3000 (NH), 1670 (C=O) and 1615, 1525, 1500 (aromatic C=C); δ_H([$^2H_6$]DMSO) **25**: 10.95 (br, OH), 9.70 (br, OH), 8.38 (br, NH_3), 7.33 (d, J = 7.3 Hz, 1 H, H2), 6.82 (d, J = 12.8 Hz, 1 H, H5) and 4.24 (br, CH_2); **26**: 11.01 (br, OH), 9.56 (br, OH), 8.41 (br, NH_3), 7.34 (dd, J = 8.8, 8.0 Hz, 1 H, H6), 6.87 (dd, J = 8.8, 1.1 Hz, 1 H, H5) and 4.30 (d, J = 2.3 Hz, 2 H, CH_2); δ_C([$^2H_6$]DMSO) **25**: 188.0 (d, J = 4.4 Hz, CO),

* Sodium 3-trimethylsilylpropanesulfonate.

156.9 (d, J = 247.2 Hz, C-6), 153.6 (d, J = 12.7 Hz, C-4), 142.6 (s, C-3), 113.9 (d, J = 4.3 Hz, C-2), 112.1 (d, J = 13.7 Hz, C-1), 103.2 (d, J = 27.6 Hz, C-5) and 47.3 (d, J = 13.5 Hz, CH_2); **26**: 188.6 (d, J = 3.6 Hz, CO), 154.0 (d, J = 6.7 Hz, C-4), 152.6 (d, J = 250.3 Hz, C-2), 133.4 (d, J = 14.3 Hz, C-3), 120.5 (d, J = 3.1 Hz, C-6), 114.2 (d, J = 10.5 Hz, C-1), 111.7 (s, C-5) and 47.1 (d, J = 11.7 Hz, CH_2); δ_F([$^2H_6$]DMSO; internal C_6F_6) **26**: −130.73 (d, J = 7.2 Hz) [Found: **25**, C, 43.8; H, 3.9; N, 6.35; Cl, 15.5; **26**, C, 44.15; H, 4.3; N, 6.5; Cl, 14.8. Calc. for $C_8H_9ClFNO_3$ (M = 221.62): C, 43.36; H, 4.09; N, 6.32; Cl, 16.00%].

General Method for the Preparation of **23**, **24**.—A solution of **19** (1 g, 3 mmol) (or **20**) in 60 cm^3 (20 cm^{-3}) abs. CH_2Cl_2 was cooled to −60 °C under a nitrogen atmosphere and stirred. After addition of BBr_3 (9 cm^3; 9 mmol), (1 mmol dm^{-3} solution in CH_2Cl_2), the solutions turned dark red. Stirring was continued for 10 min at −60 °C and for 2 h at room temperature. The reaction mixtures were hydrolysed at 0 °C and the water layer was extracted several times with ethyl acetate. The combined organic layers were thoroughly washed with water and dried with $MgSO_4$. After evaporation **23** was recrystallized from ethanol–toluene 1:2 to yield 0.76 g (80%), m.p. 258–259 °C and **24** from methanol, yield 0.80 g (85%), m.p. 244–246 °C. ν_{max}/cm^{-1} **23**: 3400 (OH), 3050 (Ar–H), 2950 (aliphatic CH), 1775, 1700 (Imid-C=O), 1690 (C=O) and 1625, 1515 (C=C); **24**: 3400–3300 (OH), 1770, 1710 (Imid-C=O), 1685 (C=O) and 1615, 1600, 1510 (C=C); m/z **23**: 315 (7%, M^+), 155 (100), 149 (39), 77 (10), 76 (24) and 43 (43); **24**: 315 (6%, M^+), 155 (100), 104 (6), 77 (7) and 76 (7); δ_H([$^2H_6$]DMSO) **23**: 10.09 (br, OH), 7.96–7.86 (m, 4 H, ArH), 7.23 (d, J = 7.2 Hz, 1 H, H2), 6.73 (d, J = 12.6 Hz, 1 H, H5) and 4.87 (d, J = 3.6 Hz, 2 H, CH_2); **24**: 10.17 (br, OH), 7.92 (m, 4 H, ArH), 7.30 (t, J = 8.2 Hz, 1 H, H6), 6.76 (d, J = 8.7 Hz, 1 H, H5) and 4.94 (d, J = 2.8 Hz, 2 H, CH_2); δ_C([$^2H_6$]DMSO) **23**: 188.3 (d, J = 5.4 Hz, CO), 167.7 (s, CO–N), 157.1 (d, J = 247.9 Hz, C-6), 153.0 (d, J = 12.4 Hz, C-4), 142.2 (s, C-3), 134.8 (s, C-4′, C-5′), 131.2 (s, C-1′, C-2′), 123.3 (s, C-3′, C-6′), 114.0 (d, J = 4.3 Hz, C-2), 112.5 (d, J = 14.5 Hz, C-1), 103.3 (d, J = 27.7 Hz, C-5) and 46.9 (d, J = 13.6 Hz, CH_2); **24**: 188.4 (d, J = 4.8 Hz, CO), 167.5 (s, CO–N), 153.8 (d, J = 7.0 Hz, C-4), 152.6 (d, J = 249.4 Hz, C-2), 134.8 (s, C-4′, C-5′), 133.5 (d, J = 14.7 Hz, C-3), 131.6 (s, C-1′, C-2′), 123.4 (s, C-3′, C-6′), 120.5 (d, J = 4.8 Hz, C-6), 114.6 (d, J = 11.3 Hz, C-1), 111.7 (s, C-5) and 46.8 (d, J = 11.3 Hz, CH_2) [Found: **23**, C, 61.0; H, 3.25; N, 4.2; **24**, C, 61.2; H, 3.3; N, 4.35. Calc. for $C_{16}H_{10}FNO_5$ (M = 315.26): C, 60.96; H, 3.20; N, 4.44%].

General Method for the Preparation of **27**, **28**.—**25** or **26** (0.74 g, 3 mmol) in 30 cm^3 methanol were hydrogenated at room temperature with Pt. The catalyst was filtered off and methanol evaporated off. The white residue of **27** was recrystallized from water–methanol to yield 0.6 g (88.6%), which decomposed at 146–149 °C; **28** was recrystallized from methanol to yield 0.5 g (74%), which decomposed at 135–137 °C. If **28** was occasionally obtained as an oily residue upon which it was dissolved in methanol; subsequent addition of ether resulted in a crystallization. ν_{max}/cm^{-1} **27**: 3400–3000br (OH, NH) and 1620, 1580, 1500 (C=C); **28**: 3500, 3400 (OH), 3100–3000 (NH), 2960, 2940 (aliphatic CH) and 1615, 1500 (C=C); δ_H([$^2H_6$]DMSO) **27**: 9.47 (br, ArOH), 9.01 (br, ArOH), 8.09 (br, NH_3), 6.85 (d, J = 7.5 Hz, 1 H, H2), 6.57 (d, J = 11.4 Hz, 1 H, H5), 6.00 (d, J = 4.1 Hz, 1 H, OH), 4.93 (dt, J = 9.6, 3.4 Hz, 1 H, CH), 2.95 (dd, J = 12.8, 3.4 Hz, 1 H, CH_2) and 2.78 (dd, J = 12.8, 9.6 Hz, 1 H, CH_2); **28**: 6.71 (t, J = 8.3 Hz, 1 H, H6), 6.62 (dd, J = 8.5, 1.0 Hz, 1 H, H5), 4.93 (dd, J = 9.4, 3.0 Hz, 1 H, CH), 2.91 (dd, J = 12.7, 3.2 Hz, 1 H, CH_2) and 2.80 (dd, J = 12.5, 9.5 Hz, 1 H, CH_2); δ_C([$^2H_6$]DMSO) **27**: (62.896 MHz) 151.9 (d, J = 234.2 Hz, C-6), 145.8 (d, J = 11.4 Hz, C-4), 141.8 (s, C-3), 117.8 (d, J = 15.2 Hz, C-1), 113.5 (d, J = 5.7 Hz, C-2), 102.9 (d, J = 25.7 Hz, C-5), 63.0 (s, CH) and 44.7 (s, CH_2); **28**: (100.62 MHz) 149.2 (d, J = 238.8 Hz, C-2), 147.0 (d, J = 5.4 Hz, C-4), 133.0 (d, J = 14.4 Hz, C-3), 119.5 (d, J = 11.9 Hz, C-1), 116.0 (d, J = 5.0 Hz, C-6), 111.0 (s, C-5), 63.6 (s, CH) and 44.7 (s, CH_2); δ_F([$^2H_6$]DMSO; internal C_6F_6) **27**: −130.59 (dd, J = 11.3, 7.5 Hz); **28**: −141.78 (d, J = 7.3 Hz) [Found: **27**, C, 42.45; H, 5.2; N, 6.05; Cl, 15.75; **28**, C, 42.3; H, 5.3; N, 6.0; Cl, 15.65. Calc. for $C_8H_{11}ClFNO_3$ (M = 223.63): C, 42.97; H, 4.96; N, 6.26; Cl, 15.85%].

3,6-Difluoropyrocatechol **b** was prepared according to the literature.[5] 3,4-Difluoropyrocatechol **a** was synthesized from 3,4-difluoroanisole in analogy to **b**.

Analytical data of 3,4-difluoroguaiacol and 3,4-difluoropyrocatechol **a**: 3,4-Difluoroguaiacol δ_H(90 MHz; $CDCl_3$) 6.78–6.42 (m, 2 H, ArH), 5.54 (br, OH) and 3.86 (s, 3 H, OCH_3); **a**, δ_H 400 MHz; ([$^2H_6$]DMSO) 9.30 (s, 2 H, OH), 6.47 (dt, 10.5, 9.2 Hz, 1 H, H5) and 6.37 (ddd, J = 9.2, 5.3, 2.2 Hz, 1 H, H6); 3,4-Difluoroguaiacol δ($CDCl_3$) 146.2 (dd, J = 240.0, J = 10.5 Hz, C-4), 144.0 (m, not resolved, C-1), 139.6 (dd, J = 244.5, 16.5 Hz, C-3), 135.2 (dd, J = 10.5, 3.0 Hz, C-2), 105.5 (d, J = 18.8 Hz, C-5), 104.7 (dd, J = 7.6, 2.8 Hz, C-6) and 56.4 (s, OCH_3); **a** δ([$^2H_6$]DMSO) 144.3 (dd, J = 234.4, 11.1 Hz, C-4), 143.5 (s, C-1), 140.5 (dd, J = 238.9, 15.3 Hz, C-3), 135.0 (dd, J = 13.2, 2.6 Hz, C-2), 109.2 (dd, J = 7.8, 2.8 Hz, C-6), 104.9 (dd, J = 17.9, 2.8 Hz, C-5) [Found: 3,4-difluoroguaiacol (M = 160.12), C, 52.8; H, 3.77. Calc. for $C_7H_6F_2O_2$: C, 52.52; H, 3.77%] [Found: **a** (M = 146.09): C, 49.5; H, 2.7. Calc. for $C_6H_4F_2O_2$: C, 49.33; H, 2.76%].

2,3,5-Trifluoro-1,4-dihydroxybenzene **c** and its precursor 2,3,5-trifluoro-4-methoxyphenol are hitherto unknown and were synthesized from 2,3,5-trifluoroanisole[15] in analogy to **a** and **b**.[5] Analytical data: 2,3,5-Trifluoro-4-methoxyphenol δ_H($CDCl_3$) 5.68 (ddd, J = 9.7, 7.3, 2.4 Hz, 1 H, ArH), 5.17 (s, br, OH) and 3.84 (s, 3 H, OCH_3); **c** δ_H([$^2H_6$]acetone) 8.84 (s, OH), 8.64 (s, OH) and 6.65 (ddd, J = 12.0, 7.8, 2.6 Hz, ArH); 2,3,5-Trifluoro-4-methoxyphenol δ_C($CDCl_3$) 146.8 (dt, J = 237.7, 5.7 Hz, C-5), 141.8 (ddd, J = 243.5, 13.5, 7.4 Hz, C-3), 141.1 (dt, J = 10.1, 6.5 Hz, C-1), 138.7 (ddd, J = 244.6, 12.7, 4.3 Hz, C-2), 127.6 (dd, J = 17.9, 13.3 Hz, C-4), 96.8 (dd, J = 24.0, 2.5 Hz, C-6) and 57.2 (s, OCH_3); **c** δ_C([$^2H_6$]acetone) 148.8 (ddd, J = 236.8, 6.4, 3.1 Hz, C-5), 143.4 (ddd, J = 241.1, 13.0, 8.4 Hz, C-3), 138.9 (ddd, J = 237.9, 12.7, 4.3 Hz, C-2), 138.7 (dt, J = 11.8, 3.0 Hz, C-1), 128.3 (dd, J = 18.1, 13.5 Hz, C-4) and 100.6 (dt, J = 23.2, 2.5 Hz, C-6) [Found: 2,3,5-trifluoro-4-methoxyphenol (M = 178.11), C, 47.1; H, 2.8. Calc. for $C_7H_5F_3O_2$: C, 47.20; H, 2.83%] [Found: **c** (M = 164.08), C, 43.5; H, 1.6. Calc. for $C_6H_3F_3O_2$: C, 43.92; H, 1.84%].

General Method for the Preparation of **d** *and* **e**.—**17** or **18** (1.5 g, 5.4 mmol) was added in small portions to a solution of 1.4 cm^3 (10.8 mmol) freshly distilled diethylamine in 15 cm^3 abs. isopropyl alcohol. The reaction mixtures were stirred for 6 h and then left overnight at room temperature. The solutions were acidified with concentrated HCl and kept in a freezer. After a few days the crystals that formed were sucked off. The products were identified as 6-fluoroveratric acid and 2-fluoroveratric acid. Recrystallization from CH_2Cl_2 (**d**) and from water–methanol (**e**) yielded 0.16 g and 0.22 g, respectively, with m.p. 200–202 °C and 185–187 °C, respectively.

A solution of each of the fluorinated veratric acids (80 mg, 0.4 mmol) in CH_2Cl_2 were cooled to −80 °C and BBr_3 (1.2 cm^3; 1 mol dm^{-3} solution in CH_2Cl_2), was added under a nitrogen atmosphere. The reaction mixtures were stirred overnight at room temperature. Hydrolysation at 0 °C led to precipitates, which were dissolved in ether. The organic phases were washed

with water and dried with $MgSO_4$. Recrystallization of the crude products from methanol yielded 54 mg (79.2%) of **d**, m.p. 190–193 °C and 50 mg (72.7%) of **e**, m.p. 185–187 °C. ν_{max}/cm^{-1} 6-fluoroveratric acid: 3000–2500 (OH), 1690 (C=O) and 1615, 1520 (aromatic C=C); **d**: 3550–2500 (OH), 1685 (C=O) and 1630, 1620, 1530 (C=C); 2-fluoroveratric acid: 3000–2800 (OH), 1700 (C=O) and 1610, 1580, 1505 (C=C); *m/z* 6-fluoroveratric acid: 200 (100%, M^+), 185 (28), 183 (19) **d**: 172 (34, M^+), 155 (100) and 127 (6); 2-fluoroveratric acid: 200 (100%, M^+), 185 (27) and 183 (12); 6-fluoroveratric acid: $\delta_H([^2H_6]DMSO)$ 12.92 (s, 1 H, COOH), 7.30 (d, J = 7.1 Hz, 1 H, H2), 6.97 (d, J = 12.5 Hz, 1 H, H5), 3.83 (s, 3 H, OCH_3) and 3.77 (s, 3 H, OCH_3); **d**: $\delta(CD_3OD)$ 7.22 (d, J = 7.2 Hz, 1 H, H2) and 6.46 (d, J = 12.0 Hz, 1 H, H5); 2-fluoroveratrum acid: $\delta_H([^2H_6]DMSO)$ 12.95 (s, 1 H, COOH), 7.61 (t, J = 8.3 Hz, 1 H, H6), 6.98 (dd, J = 9.1, 1.6 Hz, 1 H, H5), 3.89 (s, 3 H, OCH_3) and 3.78 (s, 3 H, OCH_3); **e**: $\delta_H(CD_3OD)$ 7.22 (dd, J = 8.7, 7.8 Hz, 1 H, H6) and 6.61 (dd, J = 8.8, 1.7 Hz, 1 H, H5); 6-fluoroveratric acid: $\delta_C([^2H_6]DMSO)$ 164.6 (d, J = 3.9 Hz, CO_2H), 156.7 (d, J = 251.6 Hz, C-6), 153.3 (d, J = 10.3 Hz, C-4), 144.6 (s, C-3), 112.8 (s, C-2), 109.2 (d, J = 10.9 Hz, C-1), 101.1 (d, J = 28.7 Hz, C-5), 56.2 (s, OCH_3) and 55.9 (s, OCH_3); **d**: 165.6 (d, J = 3.0 Hz, CO_2H), 156.5 (d, J = 248.5 Hz, C-6), 151.8 (d, J = 12.1 Hz, C-4), 142.1 (d, J = 2.0 Hz, C-3), 117.6 (d, J = 2.0 Hz, C-2) and 104.5 (d, J = 26.2 Hz, C-5); 2-fluoroveratric acid: 164.4 (d, J = 2.6 Hz, CO_2H), 157.0 (d, J = 4.5 Hz, C-4), 155.3 (d, J = 256.2 Hz, C-2), 136.8 (d, J = 14.9 Hz, C-3), 126.5 (s, C-6), 112.3 (d, J = 9.4 Hz, C-1), 107.7 (d, J = 2.2 Hz, C-5), 60.9 (s, OCH_3) and 56.3 (s, OCH_3); **e**: 165.5 (d, J = 3.0 Hz, CO_2H), 153.1 (d, J = 252.6 Hz, C-2), 152.4 (d, J = 6.0 Hz, C-4), 134.4 (d, J = 15.1 Hz, C-3), 123.4 (d, J = 2.0 Hz, C-6) and 111.6 (d, J = 9.1 Hz, C-1), 111.4 (d, J = 3.0 Hz, C-5) [Found: 6-fluoroveratic acid, C, 53.85; H, 4.4; 2-fluoroveratric acid: C, 53.65; H, 4.5. Calc. for $C_9H_9FO_4$ (M = 200.17): C, 54.00; H, 4.53%].

Acknowledgements

This work was supported by the *Fonds der Chemischen Industrie* and the *Deutsche Forschungsgemeinschaft*.

References

1 M. R. C. Gerstenberger and A. Haas, *Angew. Chem.*, 1981, **93**, 659.
2 J. Mann, *Chem. Soc. Rev.*, 1987, **16**, 381.
3 G. Firnau, R. Chirakal and E. S. Garnett, *J. Nucl. Med.*, 1984, **25**, 1228.
4 J. Corse and L. L. Ingraham, *J. Org. Chem.*, 1951, **16**, 1345.
5 D. L. Ladd and J. Weinstock, *J. Org. Chem.*, 1981, **46**, 203.
6 H. G. Kuivila, *J. Am. Chem. Soc.*, 1954, **76**, 870.
7 H. Meerwein in *Houben Weyl* **6/3** (1965) 63, 4. Aufl., Thieme, Stuggart.
8 H. Günther, *NMR-Spektroskopie*, Thieme, Stuttgart, 1992.
9 T. Schaefer, J. Peeling and T. A. Wildman, *Org. Magn. Reson.*, 1984, **22**, 477.
10 L. C. Hsee and D. J. Sardella, *Magn. Reson. Chem.*, 1990, **28**, 688.
11 R. H. Contreras, C. G. Giribet, M. A. Natiello, J. Perez, I. D. Rae and J. A. Weigold, *Aust. J. Chem.*, 1985, **38**, 1779.
12 J. F. W. McOmie, M. L. Watts and D. E. West, *Tetrahedron*, 1960, **24**, 2289.
13 K. L. Kirk, D. Cantacuzene, Y. Nimitkitpaisan, D. McCulloh, W. L. Padgett, J. W. Daly and C. R. Creveling, *J. Med. Chem.*, 1979, **22**, 1493.
14 G. Deuschle, *Dissertation, Universität Tübingen*, 1992.
15 J. Burdon and W. B. Hollyhead, *J. Chem. Soc.*, 1965, 6326.
16 C. Kaiser and A. Burger, *J. Am. Chem. Soc.*, 1957, **79**, 4365.
17 M. Mäurer, K. Scheffler and H. B. Stegmann, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 588.
18 H. B. Stegmann, H. Dao-Ba, K. Stolze and K. Scheffler, *Fresenius Z. Anal. Chem.*, 1985, **322**, 430.
19 G. A. Abakumov, L. G. Abakumov, V. A. Cherkasov and V. I. Nivodchikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, **5**, 1098.
20 H. Kurreck, B. Kirste and W. Lubitz, *Electron Nuclear Double Resonance Spectroscopy of Radicals in Solution*, VCH, D-6940 Weinheim, Germany, 1988.
21 K. Ulmschneider, *Dissertation, Tübingen*, 1977.
22 H. B. Stegmann, K. Stolze and K. Scheffler, *Z. Naturforsch., Teil B*, 1986, **41**, 776–780.
23 D. Klotz, T. Jülich, G. Wax and H. B. Stegmann, in *Landolt-Börnstein. Zahlenwerte und Funktionen aus Naturwissenschaft und Technik*, Neue Serie II/7g, Springer, Berlin-Heidelberg-New York, 1989.
24 H. B. Stegmann, K. Scheffler, U. Weber and P. Schuler, *J. Magn. Reson.*, 1983, **54**, 521.

Paper 3/05166H
Received 26*th August* 1993
Accepted 15*th October* 1993