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SOME 2-FLUOROETHYLAMINES DERIVED FROM HYDROCINNAMIC ACID, PHENYLPYRUVIC ACID AND DL-PHENYLALANINE[1]

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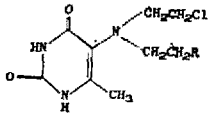
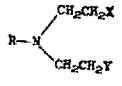
Abstract—Fluorine-containing nitrogen mustards attached to hydrocinnamic acid, phenylpyruvic acid and D,L-phenylalanine as carrier groups have been synthesized. The N-(2-chloroethyl)-N-(2'-fluoroethyl)amines are obtained by alkylation of the sodium salts of N-(benzyloxycarbonyl)amines with 2-fluoroethyl *p*-toluenesulfonate or 2-bromofluorethane, removal of the benzyloxycarbonyl group, followed by hydroxyethylation and chlorination. The bis(2-fluoroethyl)amines are obtained by heating the bis(2-*p*-toluenesulfonyloxyethyl)amines with potassium fluoride in a suitable solvent. By these reactions, methyl *m*-aminohydrocinnamate was converted to the chlorofluoro mustard XIX and the bis-fluoro mustard XX. Starting with aniline, the above reactions, in conjunction with the Vilsmeier-Haack reaction, afforded the benzaldehyde mustards VII and VIII. These are converted to the corresponding azlactones. A two-step hydrolysis of the azlactones afforded the chlorofluoro mustard IXA and the bisfluoro mustard IXB of phenylpyruvic acid. Reduction of the azlactone with zinc and acid, followed by hydrolysis, afforded the corresponding D,L-phenylalanine mustards XIIIA and XIIIB.

A REMARKABLE clinical application of the drug "ftorpan" (IA),[2] a 2-fluoroethylamine type of nitrogen mustard, has been reported. This has aroused our interest in the preparation of other fluorine-containing mustards for comparison with the corresponding chlorine-containing nitrogen mustards. The latter type (IIA) of mustard has been



IA, R = F
IB, R = Cl



IIA, X = Y = Cl
IIB, X = Cl; Y = F
IIC, X = Y = F

extensively investigated for cancer chemotherapy. Clinical trials have been made with a number of type IIA mustards which contain the appropriate R as a carrier group to impart selectivity. Among these may be mentioned dopan[3] (IB), sarcolysin[3] [IIA, R = 3-(*p*-phenyl)alanine] and chlorambucil[3] [IIA, R = 4-(*p*-phenyl)butyric acid]. It seems pertinent to extend the comparison of IA with IB to other mustards of types IIA, IIB and IIC.

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[2] L. P. Larionov, M. D. Chadakova and E. I. Arkhangel'skaia, Vop. Onkol. 7, (1961); *Cancer Chemotherapy Abstr.* 2[8] 872 (1961).

[3] R. W. Ihndris, *Cancer Chemotherapy Reports* **28**, 67 (1963).

The synthesis of the fluorine-containing mustards of types IIB and IIC appears to be more difficult than that of the chlorine-containing mustards, especially if R is to contain one or more functional groups. A number of bis(2-fluoroethyl)amines[4,5,6a] and 2-chloroalkyl-2′-fluoro-ethylamines[7] has been prepared by heating a large excess of 2-bromofluoroethane or 2-fluoroethyl toluene-*p*-sulfonate with the appropriate amine with or without an acid acceptor. The yields were often low and the methods may not be suitable for use with complex molecules. Most recently, the use of bis(2-fluoroethyl)amine as a precursor of N-bis(2-fluoroethyl)benzylamines was demonstrated.[6b] We were interested in developing synthetic methods with broad scope applicable to the synthesis of molecules as complex as the title compounds. Some results are reported here.

For synthesizing the 2-chloroethyl-2′-fluoroethylamines, the fluoroethyl group was introduced by alkylation of a primary amine suitably activated to allow easy reaction and blocked to prevent dialkylation. Removal of the activating and blocking group, followed by reaction of the N-(2-fluoroethyl)amine with ethylene oxide, then chlorination, afforded the desired 2-chloroethyl-2′-fluoroethylamine.

Thus the activated amine, N-(benzyloxycarbonyl)aniline,[8] was readily alkylated to give the N-(fluoroethyl)amide III as an unanalyzed oil by treatment with sodium hydride and 2-fluoroethyl *p*-toluenesulfonate or 2-bromofluoroethane in N,N-dimethylformamide at room temperature. Deblocking with hydrogen bromide in glacial acetic acid gave N-(2-fluoroethyl)aniline (IV), characterized as the crystalline hydrochloride salt. The overall yield of the hydrochloride of IV was over 80% from aniline. The literature[6a] yield was 15%. Hydrogenolysis of III over Pd-C at one atmosphere also afforded IV in good yields. There was no evidence of hydrogenolysis of the fluorine.

Reaction of IV with ethylene oxide gave crude, undistilled N-(2-fluoroethyl)-N-(2′-hydroxyethyl)aniline[7] (V) in suitable purity for the next reaction. The 65–70% yield from aniline compared favorably with the previously reported[7] yield of 25% of distilled product obtained by heating 2-hydroxyethylaniline, 2-bromofluoroethane and soda at 90°. By the modified Vilsmeier-Haack reaction with phosphoryl chloride and N,N-dimethylformamide, V was converted to the aldehyde VII[9] as an oil, which was characterized as the crystalline anil XIA and the azlactone XA.

The azlactone XA was readily hydrolyzed to the desired phenylpyruvic mustard IXA by a two-step treatment with methanolic hydrogen chloride followed by concentrated hydrochloric acid. This procedure[10a] was an improvement over that used in the

[4] A. F. Childs, L. J. Goldworthy, G. F. Harding, F. E. King, A. W. Nineham, W. L. Norris, S. G. P. Plant, B. Selton and A. L. L. Tomposett, *J. Chem. Soc.* 2174 (1948).

[5] E. Wilson and M. Tishler, *J. Amer. Chem. Soc.* **73**, 3635 (1951).

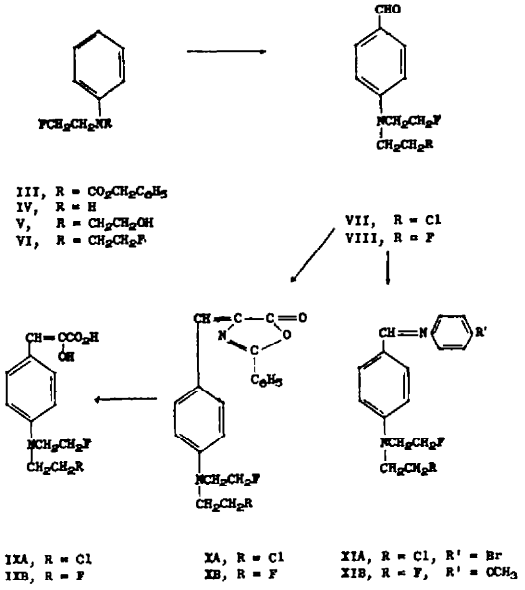
[6a] V. G. Nemets and G. L. Epshtein, *Izv. Vysshikh Uchebn, Zavedenii Khim: Khim. Tekhnol.* **5**, 101 (1962); *Chem. Abstr.* **58**, 3297 (1963); [b] G. R. Pettit and R. L. Smith, *Canad. J. Chem.* **42**, 572 (1964).

[7] V. G. Nemets and G. G. Tsybaeva, *Trudy Leningrad. Tekhnol. Inst. im. Kensoveta.* **60**, 49 (1960); *Chem. Abstr.* **55**, 20943 (1961).

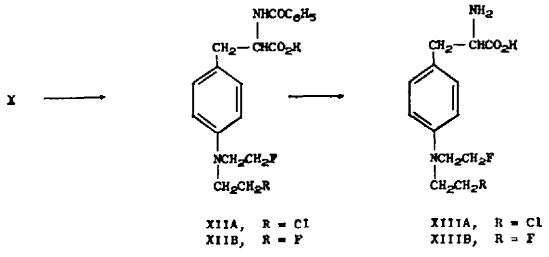
[8] H. V. Soden and W. Rojahn, *Ber. Dtsch. Chem. Ges.* **34**, 2809 (1901).

[9] The synthesis was patterned after that of *p*-[bis(2-chloroethyl)amino]benzaldehyde. See R. H. Wiley and G. Irick, *J. Org. Chem.* **26**, 593 (1961).

[10a] This modification was developed after publication of 10*b*. [b] A. P. Martinez, W. A. Skinner, W. W. Lee, L. Goodman and B. R. Baker, *J. Amer. Chem. Soc.* **82**, 6050 (1960).



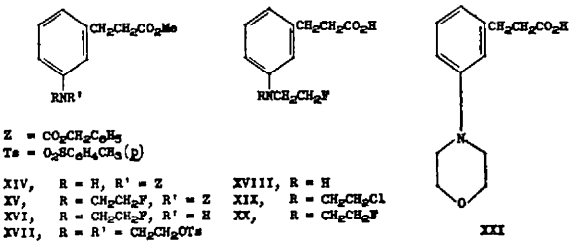
synthesis of the bis-chloro analog[11,10b] of IXA in which the azlactone was first converted to methyl α-benzamido-*p*-[bis(2-chloroethyl)amino]cinnamate,[11] and this was given the two-step acid treatment[10b] to afford the bis-chloro mustard of phenylpyruvic acid. The crystalline, yellow-green IXA was enolic, like the bis-chloro analog, as shown by its IR spectrum. The overall yield of IXA from aniline was 17%. This was comparable to the yields for the bis-chloro analog of IXA[10,11] and was quite satisfactory when compared with the yields reported for some less complex fluoroethylamines.[4,7]



The azlactone XA was readily reduced and opened to afford the benzamide XIIA by treatment with zinc dust in a mixture of acetic acid and hydrochloric acid in a fashion similar to that for the bis-chloro analog.[12] The benzamide XIIA was treated with hot hydrochloric acid in order to obtain the D,L-phenylalanine mustard XIIIA.

The conditions used to prepare the fluoroethylamine IV were mild enough to be applied in the hydrocinnamic acid series. Thus the benzyloxycarbonylamide (XIV), prepared from methyl *m*-aminohydrocinnamate,[13] was converted to the fluoroethylamide XV, and then the fluoroethylamine XVI, characterized as the hydrochloride.

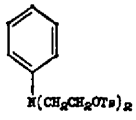
[11] F. D. Popp, *J. Org. Chem.* **26**, 3020 (1961).
[12] V. N. Konyukhov and Z. V. Pushkareva, *Chem. Abstr.* **58**, 2501 (1963).
[13] W. A. Skinner, H. F. Gram, C. W. Mosher and B. R. Baker, *J. Amer. Chem. Soc.* **81**, 4639 (1959).



Hydroxyethylation followed by reaction with phosphoryl chloride gave the unisolated ester of XIX which was hydrolyzed during the workup to afford the final mustard, *m*-[N-(2-chloroethyl)-N-(2′-fluoroethyl)amino]hydrocinnamic acid (XIX).

For the synthesis of bis(2-fluoroethyl)amines, the displacement of the chlorine by fluoride was briefly examined using *m*-[bis(2-chloroethyl)-amino]hydrocinnamic acid or the methyl ester. This approach was not promising because of the difficulty in determining the extent of reaction and in separating the products. However, displacement of the *p*-toluenesulfonyloxyl group of methyl *m*-[bis(2-*p*-toluenesulfonyloxyethyl)-amino]hydrocinnamate (XVII) could be followed by changes in the IR spectrum. Thus heating a mixture of dry potassium fluoride and XVII in diethylene glycol for 2 hr caused complete displacement of the *p*-toluenesulfonyloxy groups. There was evidence of serious side reactions such as the formation of hydroxyl-containing products and of transesterification products. Nevertheless, by careful saponification and workup of the reaction mixture, it was possible to isolate *m*-[bis(2-fluoroethyl)-amino]hydrocinnamic acid (XX) in low yield. Acid hydrolysis gave no crystalline product. When N,N-dimethylformamide was used as the solvent in the displacement of the *p*-toluenesulfonyloxy groups, the only product isolated after hydrolysis was *m*-(1-morpholino)hydrocinnamic acid (XXI).[14] This initial study of toluenesulfonyloxy displacement was complicated by the instability of XVII.

Displacement of the *p*-toluenesulfonyloxy groups from a simpler model, N,N-bis (2-*p*-toluenesulfonyloxyethyl)aniline (XXII) was therefore studied. This compound had the advantages of being crystalline and stable. Reproducible results could be obtained with the same batch of XXII over a period of at least four weeks.



XXII

A study of various solvents[15] indicated that in ethylene carbonate, N-methyl-2-pyrrolidone, a mixture of these two or in N,N-dimethylformamide, reaction with potassium fluoride at 150° for 30 min was sufficient to completely displace the toluenesulfonyloxy groups. N-methyl-2-pyrrolidone, either alone or as a mixture with

[14] G. R. Pettit and R. L. Smith[65] have similarly observed the formation of some N-(*p*-toluenesulfonyl)-morpholine when N,N-bis(2-mesyloxyethyl)toluenesulfonamide was treated with potassium fluoride. We wish to thank Dr. Pettit for his kindness in making available their manuscript before its publication.

[15] Some of the solvents studied by J. T. Maynard, *J. Org. Chem.* **28**, 112 (1963), and those discussed by A. J. Parker, *Quart. Revs.* **16** (1962).

ethylene carbonate, appeared to be the solvent of choice. It gave the highest yield of the purest product VI, as indicated by gas chromatography. With ethylene carbonate alone, gelling occurred during the reaction, making the solvent impractical for large scale runs. With N,N-dimethylformamide, the yield of VI was lower and gas chromatography showed an additional by-product. In this solvent, unlike compound XVII, XXII did not give a morpholine as the principal product. With 1-acetoxy-2-ethoxyethane, the displacement did not occur with heating at 150° for 30 min. Surprisingly, the starting XXII could be recovered in 30% yield as a crystalline material. With diethylene glycol, the yield of VI was very low; the bulk of the product was material containing hydroxyl groups as shown by infrared spectra.

Reaction of VI with N,N-dimethylformamide and phosphoryl chloride gave the aldehyde VIII, a crystalline solid, in excellent yield; VIII was also characterized as the anil XIB in 73% yield.

In exactly the same manner as for the aldehyde VII, the bis-fluoro analog VIII was converted to the azlactone XB and thence to *p*-[bis-(2-fluoroethyl)amino]phenylpyruvic acid (IXB) and to the *p*-[bis(2-fluoroethyl)amino]-D,L-phenylalanine (XIIIB). Unlike the bis-chloro and the chlorofluoro analogs, the crystalline azlactone XB was not solvated. The bis-fluoro mustards IXB and XIIIB were less stable and more difficult to crystallize and purify than the chlorofluoro analogs. It was important, therefore, to have the immediate precursors of IXB and XIIIB at a high state of purity before the final hydrolysis.

The aldehydes VII and VIII are versatile intermediates. Their conversion into fluoro mustards of cinnamic acid and of other products by condensation with active methylene compounds is under investigation in these laboratories.

EXPERIMENTAL[16]

N-(2-Fluoroethyl)aniline hydrochloride (IV·HCl). To a stirred solution of 12·0 g (53 mmoles) N-benzyloxycarbonylaniline[8] in 110 ml freshly distilled N,N-dimethylformamide was added 3·20 g (72 mmoles) 54% NaH suspension in mineral oil. (The suspension was prewashed with 25 ml pet ether, b.p. 30–60°, to remove most of the oil.) The reaction mixture was stirred at room temp for 15 min while protected from moisture. A solution of 13·1 g (60 mmoles) 2-fluoroethyl *p*-toluenesulfonate in 20 ml N,N-dimethylformamide was added. The mixture was stirred at room temp for 4 hr, or longer if necessary, until the IR spectrum of a sample indicated that the reaction was complete (no more absorption at 3·05 μ (N-H) and 6·40 μ (amide II). The reaction mixture was evaporated to dryness *in vacuo* (60°/1 mm). A 50 ml portion of toluene was added, and the mixture was evaporated to dryness *in vacuo*. This was repeated once more. The residue was partitioned between 200 ml each of water and methylene chloride. The organic layer was separated, washed with water, dried and evaporated *in vacuo* to leave a yellow oil weighing 15·0 g (100%) of III; $\lambda_{max(\mu)}^{film}$ 5·85 (C=O). The IR spectrum indicated there was no unreacted 2-fluoroethyl *p*-toluenesulfonate left.

A cooled solution of 60 ml of 30–32% HBr in glacial acetic acid was added rapidly to 12·1 g (44·4 mmoles) of III with stirring and cooling (−5°). The solution was stirred for 10 min, the cooling bath was removed, and stirring was continued for 60 min. The reaction mixture was poured into a well-stirred mixture of 100 g Na_2CO_3, 300 ml sat. $NaHCO_3$ aq and 200 ml ether. The ether layer was separated, washed with 100 ml water, dried and saturated with anhydrous HCl. The white precipitate was collected, washed with 50 ml dry ether *in vacuo* to afford 7·59 g (97%) of IV·HCl, m.p. 158–159°.

[16] M.ps were determined with the Fisher-Johns apparatus. Paper chromatography was done by the descending technique on Whatman No. 1 paper, except for solvent A which was run on Schleicher and Schuell No. 2496 acetylated paper. The solvent systems are: A, benzene–methanol–water (2:6:1); B, n-butanol–water (saturated); C, n-butanol–acetic acid–water (5:2:3); D, 5% Na_2HPO_4 aq, pH 8·9; F,n-butanol–2N HCl (saturated).

This was of suitable purity for the next step. Recrystallization from absolute ethanol gave the analytical sample of IV·HCl. m.p. 164·5–165·5°; $\lambda_{max(\mu)}^{Nujol}$ 3·6–4·5 and 5·0 ($R_3NH_2^+$), 6·30–6·65 (aryl). The literature[6a] m.p. is 171°. (Found: C, 54·7; H, 6·31; F, 10·51; N, 7·63. Calc. for $C_8H_{10}FN$·HCl: C, 54·6; H, 6·31; F, 10·82; N, 7·98%).

For the preparation of III, the use of 2-bromofluoroethane at room temp was satisfactory, although more expensive. There was no advantage in using higher temp. In fact, the loss of volatile 2-bromofluoroethane was increased. For the conversion of III to IV·HCl, hydrogenolysis over 5% Pd—C in methyl Cellosolve containing HCl at 1 atm. was complete in 20 hr. There was no hydrogenolysis of fluorine.

N-(*2-Fluoroethyl*)-N-(*2'-hydroethyl*)*aniline* (V)[7]. A solution of 4·68 g (33·7 mmoles) of IV, regenerated from the hydrochloride salt, and 1·58 g (36 mmoles) ethylene oxide in 30 ml glacial acetic acid was stirred at room temp overnight in a stoppered flask. The solution was evaporated to dryness *in vacuo*. The residue was dissolved in 75 ml methylene chloride, washed with 75 ml sat. $NaHCO_3$ aq, then with 100 ml water. The methylene chloride was dried and evaporated *in vacuo* to afford 5·20 g (84%) of V as a light amber oil; $\lambda_{max(\mu)}^{film}$ 2·92 (O-H), 6·22, 6·60 (aryl). This product was sufficiently pure for use in the next reaction.

N,N-*Bis*(*2-fluoroethyl*)*aniline* (VI). To a stirred mixture of 35·0 g (0·60 mole) dry[17] KF suspended in 150 g ethylene carbonate-N-methyl-2-pyrrolidone (1:1) heated at 150° (bath temp) was added 68·5 g (0·140 mole) of XXII[18] in one portion. After heating and stirring at 150° for 30 min under N_2, the reaction mixture was rapidly cooled and poured into 1·6 l water and extracted with 2 portions pet ether, b.p. 65–110°, totalling 1·2 l. The organic extracts were washed with water, dried ($MgSO_4$), and evaporated at 60°/15 mm to leave 21·0 g (81%) of VI as a clear yellow oil, n_D^{25} 1·5331. Distillation afforded 17·1 g (65%) of VI, b.p. 64–70°/0·03 mm, n_D^{25} 1·5328, a colorless oil which darkens on standing, having an IR spectrum identical to that of the analytical sample.

A portion of crude oil from an earlier run was purified by preparative gas chromatography to afford the analytical sample of VI, n_D^{25} 1·5274 (this had darkened somewhat in the receiver during the overnight chromatography); $\lambda_{max(\mu)}^{Nujol}$ 6·23, 6·60 (aryl), 9·5, 9·65, 9·89, 10·04, 13·35, 14·4. No absorption at 3·0 (N—H) or 8·50 (—SO_2—). (Found: F, 20·3; N, 7·62. $C_{10}H_{13}F_2N$ requires: F, 20·5; N, 7·55%).

The hydrochloride salt was prepared by saturating an ethereal solution of distilled VI with anhydrous HCl. Recrystallization from benzene containing a trace of ethanol afforded 45% (from XXII) of VI·HCl, m.p. 80·5–81·0°; $\lambda_{max(\mu)}^{Nujol}$ 4·10 (R_3NH^+), 6·22, 6·30 and 6·64 (aryl and R_3NH^+). It moved as a single spot in solvents A and C with R_f values of 0·11 and 0·92, respectively. (Found: C, 54·7; H, 6·49; F, 17·1. $C_{10}H_{13}F_2N$·HCl requires: C, 54·3; H, 6·36; F, 17·2%).

Similar crude yields (75–81%) of VI were obtained with either ethylene carbonate or N-methyl-2-pyrrolidone. With the last solvent, the crude VI could be converted directly to the crystalline hydrochloride in 55% yield (from XXII) without distillation. The material is conveniently stored in this form.

p-[N-(*2-Chloroethyl*)-N-(*2'-fluoroethyl*)*amino*]*benzaldehyde* (VII). By the method of Wiley and Irick,[9] 20 ml (0·22 mole) $POCl_3$, 60 ml freshly distilled N,N-dimethylformamide and 10·3 g (56·3 mmoles) of V gave, after 20 min at 125°, 12·55 g (98%) of VII as an amber oil; $\lambda_{max(\mu)}^{film}$ 3·62, 5·90 (CHO). This product was sufficiently pure for further reactions.

A solution of 0·39 g (1·7 mmole) of VII and 0·29 g (1·7 mmole) *p*-bromoaniline in 20 ml of absolute ethanol was heated at reflux for 45 min, cooled and filtered to collect 0·42 g (64%) N-{*p*-[N'-(*2-chloroethyl*)-N'-(*2-fluoroethyl*)*amino*]*benzylidene*}*p-bromoaniline* (XIA), m.p. 126–127·5°. Recrystallization from absolute ethanol gave 0·32 g (49%) of XIA, m.p. 127·5–128°; $\lambda_{max(\mu)}^{Nujol}$ 6·20, 6·32, 6·37, 6·42, 12·0 (aryl and C=N). (Found: C, 53·3; H, 4·79; F, 5·02, 5·13; N, 7·02. $C_{17}H_{17}BrClFN_2$ requires: C, 53·3; H, 4·47; F, 4·95; N, 7·30%).

p-[*Bis*(*2-fluoroethyl*)*amino*]*benzaldehyde* (VIII). Prepared, using the directions for VII, in quantitative yield as a solid, m.p. 39–42°, of suitable purity for the next reaction. Recrystallization from ethanol–water gave a 76% yield of the analytically pure VIII, m.p. 45·5–46·5°, $\lambda_{max(\mu)}^{Nujol}$ 3·62, 5·95 (CHO). (Found: C, 61·9; H, 6·14; F, 18·0. $C_{11}H_{13}F_2NO$ requires: C, 61·9; H, 6·14; F, 17·8%).

[17] Anhydrous, finely divided KF is essential. It is prepared by the procedure of G. C. Finger and C. W. Kruse, *J. Amer. Chem. Soc.* **78**, 6034 (1956).

[18] G. M. Timmis, *Brit.* 662, 645 (1951); A. Cohen and R. S. Tipson, *J. Med. Pharm. Chem.* **6**, 822 (1963).

VIII was characterized by reaction with *p*-anisidine to give a 73% yield of N-{*p*-[*bis*(2-*fluoroethyl*)-*amino*]*benzylidene*}*p*-*methoxyaniline* (XIB), yellow crystals, m.p. 73·5–74°, not raised by recrystallization from ethanol; $\lambda_{max(\mu)}^{Nujol}$ 6·28, 6·40, 6·55 (aryl and C=N-), 8·49 (C-O). (Found: N, 8·46. $C_{18}H_{20}F_2N_2O$ requires: N, 8·90%).

4-{*p*-[N-(*Chloroethyl*)-N-(2′-*fluoroethyl*)*amino*]*benzylidene*}-2-*phenyl*-2-*oxazolin*-5-*one* (XA). By the literature method,[11] 16·2 g (71 mmoles) of VII was converted into 15·4 g (49%) solvated[19] azlactone XA, m.p. 60–80°; $\lambda_{max(\mu)}^{Nujol}$ 5·58, 5·62 (azlactone); it moved as one spot in solvents A and B with R_f values of 0·10 and 0·91, respectively. (Found: C, 67·4; H, 5·32; F, 4·62; N, 6·46. $C_{20}H_{18}ClFN_2O_2 \cdot \frac{1}{2}C_6H_6$ requires: C, 67·2; H, 5·15; F, 4·62; N, 6·82%).

4-{*p*-[*Bis*(2-*fluoroethyl*)*amino*]*benzylidene*}-2-*phenyl*-2-*oxazolin*-5-*one* (XB). XB was prepared like XA in 54% yield as red crystals, m.p. 130–137° from toluene–pet ether, b.p. 60–110°). It was homogeneous according to paper chromatography. The analytical sample of XB from an earlier run was crystallized from benzene; it has m.p. 138–140°; $\lambda_{max(\mu)}^{Nujol}$ 5·60, 5·65 (azlactone). It moved as a single spot in solvents A and B with R_f 0·03 and 0·92, respectively. (Found: C, 67·4; H, 5·20; F, 10·41; N, 7·28. $C_{20}H_{18}F_2N_2O_2$ requires: C, 67·4; H, 5·09; F, 10·68; N, 7·64%).

p-[N-(2-*Chloroethyl*)-N-(2′-*fluoroethyl*)*amino*]*phenylpyruvic acid* (IXA). A solution of 4·00 g (8·88 mmoles) azlactone XA in 200 ml of absolute methanol was saturated with anhydrous HCl at 0°, and then heated at reflux temp for 18 hr with protection from moisture. The solution was evaporated to dryness *in vacuo* at 45°/15 mm and finishing at 45°/0·1 mm to remove all methyl benzoate. The residue, a solid foam, was dissolved in 50 ml conc. HCl and heated at 65° for 25 min, then quickly chilled in an acetone–dry ice bath, and neutralized with a cold solution of 80 g sodium acetate trihydrate in 200 ml water. The cold mixture was extracted with one 150-ml and two 75-ml portions ether. The ether extracts were dried, concentrated *in vacuo* to about 100 ml, diluted with 1 volume toluene, then evaporated to dryness *in vacuo* at 40°, finishing at 0·5 mm. The green semi-solid residue gradually crystallized. This was triturated with 50 ml toluene–Skellysolve B (b.p. 62–70°) (1:1). The green-yellow solid was collected and dried *in vacuo* to afford 1·25 g (49%) of IXA, m.p. 138·5–140·0°. This was treated with 20 ml hot methylene chloride until all the material had changed to a bright yellow crystalline form of IXA, wt. 1·18 g (47%), m.p. 147·5–148·0°; $\lambda_{max(\mu)}^{Nujol}$ 2·88, 2·92 (OH); 3·6–4·5 (COOH), 5·99 (C=O of COOH), 6·25, 6·55 and 10·15. No suitable paper chromatography system was found. (Found: C, 54·3; H, 5·17; F, 6·20; N, 4·63. $C_{13}H_{15}ClFNO_3$ requires: C, 54·3; H, 5·25; F, 6·60; N, 4·86%).

p-[N,N-*Bis*(2-*fluoroethyl*)*amino*]*phenylpyruvic acid* (IXB). By the above procedure, 1·78 g (5·00 mmoles) bis-fluoro azlactone XB gave, after recrystallization from methylene chloride–toluene, a yield of 0·21 g (16%) pyruvic acid IXB, m.p. 156–157°; $\lambda_{max(\mu)}^{Nujol}$ 2·85, 2·90 (OH), 3·6–4·5 (COOH), 5·90, 6·00 (C=O). (Found: C, 57·7; H, 5·66; F, 13·9; N, 5·06. $C_{13}H_{15}F_2NO_3$ requires: C, 57·6; H, 5·57; F, 14·0; N, 5·17%).

N-*Benzoyl*-3-{*p*-[N-(2-*chloroethyl*)-N-(2′-*fluoroethyl*)*amino*]*phenyl*}-D,L-*alanine* (XIIA). By the literature procedure,[12] a cold (0°) solution of 34·0 g of XA in 170 ml acetic acid and 260 ml of 12N HCl was treated with 87 g of Zn at below 9° to afford 21·9 g (68%) of XIIA, white crystals, m.p. 156–157°. Two recrystallizations from 1,2-dimethyloxyethane–water (1:1) afforded the analytical sample of XIIA, m.p. 159·5–160·5°; $\lambda_{max(\mu)}^{Nujol}$ 2·97 (N—H), 5·79 (COOH), 6·14, 6·49 (amide). It moved as one spot in solvent B with R_f 0·61. (Found: C, 60·8; H, 5·68; Cl, 8·84; F, 4·83; N, 7·17. $C_{20}H_{22}ClFN_2O_3$ requires: C, 61·1; H, 5·64; Cl, 9·02; F, 4·84; N, 7·13%).

N-*Benzoyl*-3-{*p*-[*bis*(2-*fluoroethyl*)*amino*]*phenyl*}-D,L-*alanine* (XIIB). By essentially the same procedure as above, 11·4 g of XB, treated with Zn and acid at 10–15° for 1·5 hr, gave 9·3 g (81%) of XIIB, m.p. 178–179°. The analytical sample was from an earlier run and had m.p. 177·5–178·5°; $\lambda_{max(\mu)}^{Nujol}$ 2·95 (N-H), 5·80 (COOH), 6·14, 6·51 (amide). It moved as a single spot in solvents B and C with R_f values of 0·52 and 0·93, respectively. (Found: C, 63·9; H, 5·79; F, 9·64. $C_{20}H_{22}F_2N_2O_3$ requires: C, 63·8; H, 5·88; F, 10·09%).

p-[*Bis*(2-*fluoroethyl*)*amino*]*phenyl*-D,L-*alanine* (XIIIB). A solution of 1·00 g (2·86 mmoles) XIIB in 25 ml 12N HCl was heated (bath temp, 115–118°) for 5 hr. The reaction mixture was cooled in an ice bath and freed of benzoic acid by two 60 ml extractions with ether. The aqueous solution was evaporated to dryness *in vacuo* at 55°/0·1 mm to leave 0·80 g of XIIB·HCl as a white foam. This was dissolved in 15 ml water and neutralized to pH 6 with sodium acetate trihydrate. There was no immediate precipitation. The yellow solution was kept at 5° overnight, and the white crystalline precipitate

[19] The bis-chloro analog was also solvated. See Ref. 10*b*.

was collected, dried (P_2O_5) at room temp *in vacuo*, and then at 56°/0·1 mm to afford 0·43 g (58%) of XIIB, m.p. 172·5–173·5°; it was identical to the analytical sample by paper chromatography and IR spectra comparisons.

A sample of XIIIB from an earlier run was analyzed. It had m.p. 174·5–175·5°; $\lambda_{max(\mu)}^{Nujol}$ 2·90, 3·6–4·2 (RNH_3^+), 6·15 (COO^-). It moved as a single spot in solvents B and C with R_f values of 0·35 and 0·73, respectively. (Found: C, 55·5; H, 6·80; F, 13·5. $C_{18}H_{18}F_2N_2O_2 \cdot \frac{1}{2}H_2O$ requires: C, 55·5; H, 6·80; F, 13·50; N, 9·95%).

This compound was very sensitive to heat and could not be recrystallized from water. However, trituration with acetone at room temp gave XIIIB, m.p. 176–177°, still as the hemihydrate. (Found: C, 55·0; H, 6·77; F, 13·6; N, 9·69%).

p-[N-(2-*Chloroethyl*)-N-(2′-*fluoroethyl*)*amino*]*phenylalanine* (XIIIA). Treatment of XIIA with hot HCl, by the procedure used to prepare XIIIB, afforded XIIIA (80% yielded from XIIA), m.p. 173–174°. This was homogeneous by paper chromatography. Recrystallization from absolute ethanol afforded the analytical sample of XIIIA, m.p. 180–181°; $\lambda_{max(\mu)}^{Nujol}$ 3·6–4·2 (RNH_3^+), 6·15, 6·28, 6·55 (CO_2^- and aryl). It moved as a single spot in solvents B and D with R_f values of 0·40 and 0·70, respectively. (Found: C, 53·7; H, 6·42; Cl, 12·2; F, 6·39; N, 9·48. $C_{13}H_{18}ClFN_2O_2$ requires: C, 54·1; H, 6·38; Cl, 12·3; F, 6·58; N, 9·72%).

Methyl m-(*benzyloxycarbonylamino*)*hydrocinnamate* (XIV). To a stirred solution of 17·3 g (97 mmoles) methyl *m*-aminohydrocinnamate[13] in 60 ml pyridine and 160 ml methylene chloride at room temp was added 16·0 g (104 mmoles) benzyloxycarbonyl chloride in 80 ml methylene chloride. The reaction mixture was kept overnight at room temp, then washed successively with 400 ml water, 400 ml 20% HCl aq, 200 ml water, 200 ml sat. $NaHCO_3$ aq and finally with 200 ml water. The organic solution was dried and evaporated to dryness *in vacuo*, leaving 24·2 g (80%) product as a faintly yellow oil which crystallized on standing, m.p. 50–51°. Recrystallization from ether–Skellysolve B afforded 23·7 g (78%) of XIV, m.p. 52·5–53·0°; $\lambda_{max(\mu)}^{Nujol}$ 2·98 (N-H), 5·72, 5·79 (C=O of amide and ester), 6·18, 6·62 (aryl), 6·40 (amide II). It moved as a single spot with R_f 0·42 on a thin layer chromatographic plate of silica gel eluted with chloroform. (Found: C, 69·2, H, 6·25; N, 4·16. $C_{18}H_{19}NO_4$ requires: C, 69·0; H, 6·12; N, 4·47%).

Methyl m-[N-*benzyloxycarbonyl*-N-(2-*fluoroethyl*)*amino*]*hydrocinnamate* XV. By the same procedure used to prepare III, the amide XIV afforded a quantitative yield of XV as an oil whose IR spectrum indicated only a trace of unreacted N—H. This was of sufficient purity for subsequent reactions. For analysis, the oil was extracted with pet ether, b.p. 30–60°. Evaporation of the pet ether extract left 50% oil; $\lambda_{max(\mu)}^{film}$ 5·72, 5·83 (C=O of ester and amide); no absorption at 2·98 and 6·40. It moved as a single blue fluorescent spot in solvents A and B with R_f values of 0·13 and 0·95, respectively. The starting material XIV had almost the same R_f values but a different color (blue, UV absorbing). (Found: C, 66·9; H, 6·23; F, 5·35; N, 3·99. $C_{20}H_{22}NFO_4$ requires: C, 66·9; H, 6·13; F, 5·33; N, 3·90%).

Methyl m-[2-*fluoroethylamino*]*hydrocinnamate hydrochloride* (XVI·HCl). The procedure used for coverting III to IV was applied to 3·53 g (9·84 mmoles) of XV and gave 1·90 g (74%) crude hydrochloride of XVI. This was sufficiently pure for use in subsequent reactions. Regeneration of the base and reprecipitation of the hydrochloride from benzene gave 1·15 g (45%) of XVI·HCl, m.p. 104–105°; $\lambda_{max(\mu)}^{Nujol}$ 3·80, 4·05, 4·15, 4·95 ($R_2NH_2^+$), 5·78 (C=O of ester). (Found: N, 5·17; F, 7·07. $C_{12}H_{16}NFO_2 \cdot HCl$ requires: N, 5·35; F, 7·26%).

m-[N-2-*Chloroethyl*)-N-(2′-*fluoroethyl*)*amino*]*hydrocinnamic acid* (XIX). A solution of 5·00 g (22·2 mmoles) of XVI in 26 ml glacial acetic acid was allowed to react with an equimolar amount ethylene oxide to give 5·42 g (91%) methyl *m*-[N-(2-fluoroethyl)-N-(2-hydroxyethyl)amino]hydrocinnamate.

A 1·70 g (6·31 mmoles) portion methyl *m*-[N-(2-fluoroethyl)-N-(2-hydroxyethyl)amino]hydrocinnamate in 15 ml $POCl_3$ was heated in a steam bath for 30 min while protected from moisture. The hot solution was poured over 150 ml ice and water, then stirred overnight. The reaction mixture was washed with two 40 ml portions methylene chloride, neutralized with solid sodium acetate trihydrate to pH 5 and extracted with three 40 ml portions methylene chloride. These extracts were combined, dried, and evaporated *in vacuo* to leave 1·37 g (80%) of XIX as an amber oil which crystallized when scratched. Recrystallization from Skellysolve B–methylene chloride with the aid of Norit afforded 1·20 g (70%) of XIX, m.p. 76·0–76·5°, as white crystals; $\lambda_{max(\mu)}^{Nujol}$ 3·70–4·2, 5·86 (COOH); 6·25, 6·32, 6·65 (aryl); 10·0 (C—F). It moved as a single spot in solvents B and F with R_f values of 0·71 and 0·95

respectively. (Found: C, 57·1; H, 6·32; Cl, 13·22; F, 6·81. $C_{13}H_{17}ClFNO_3$ requires: C,57·0; H, 6·26; Cl, 12·95; F, 6·95%).

The use of $SOCl_2$ instead of $POCl_3$ gave much poorer yields of product.

Methyl m-[bis(2-tosyloxyethyl)amino]hydrocinnamate (XVII). To an ice-cooled, stirred solution of 3·62 g (13·3 mmoles) methyl *m*-[bis-(2-hydroxyethyl)amino]hydrocinnamate[20] in 50 ml pyridine was added 5·10 g (26·7 mmoles) *p*-toluenesulfonyl chloride. The solution was kept in the ice bath for 5 hr and in a refrigerator (about 5°) overnight. The solution was diluted with 100 ml methylene chloride, washed with four 150 ml portions water (the last wash being gradually acidified to pH 5 with HCl aq), 50 ml sat. $NaHCO_3$ aq and again with 50 ml water. The organic phase was dried and evaporated *in vacuo* at 30°, finishing at 1 mm, to afford 4·82 g (63%) viscous gum; $\lambda_{max(\mu)}^{liquid}$ 5·74 (C=O), 7·35, 8·50 (-SO_3-) and none at 2·90 (OH); R_f 0·90 in solvent H. (Found: C, 58·2; H, 6·21; S, 10·8. $C_{28}H_{33}NO_8S_2$ requires: C, 58·4; H, 5·95; S, 11·1%).

This compound was unstable and slowly decomposed when stored in a refrigerator. It should be used as soon as possible and certainly within one or two weeks after preparation.

m-[Bis(2-fluoroethyl)amino]hydrocinnamic acid (XX). A stirred suspension of 5·0 g (86 mmoles) dry KF in 8·0 ml diethylene glycol and 50 ml benzene was protected from moisture and distilled to remove about 40 ml benzene. To this was added a solution of 2·00 g (4·75 mmoles) of XVII. The bath temp was raised until all the benzene had distilled and maintained at 160–170° for 2 hr. The reaction mixture was partitioned between 50 ml methylene chloride and 150 ml water. The organic layer was washed with 150 ml water, dried, and evaporated *in vacuo* to leave 1·22 g of a light yellow oil. This contained the desired methyl *m*-[bis(2-fluoroethyl)amino]hydrocinnamate as well as hydroxyl- containing by-products, as indicated by the IR spectrum.

A solution of 1·10 g of the above oil in 4 ml of 1N methanolic NaOH and 0·20 ml water was stirred at room temp for 18 hr, then evaporated to dryness *in vacuo*. The residue was taken up in 25 ml water, washed with 25 ml portions methylene chloride and ether, acidified with 4 ml 1N HCl, and extracted with 25 ml methylene chloride. The organic extract was dried and evaporated *in vacuo* to leave 0·60 g viscous yellow oil. This oil was extracted with three 50 ml portions of Skellysolve B at reflux temp. The extracts were cooled to room temp, filtered through Celite, and then cooled in an ice bath to afford 0·20 g (18%) of XX as fine white needles, m.p. 76–77°; $\lambda_{max(\mu)}^{Nujol}$ 3·6–4·2, 5·86 (COOH), 6·24, 6·31, 6·66 (aryl), 9·99 (C-F?); it moved as a single spot in solvents B, D and E with R_f values of 0·87. 0·78 and 0·85, respectively. (Found: C, 61·1; H, 6·65; N, 5·36; F 14·6. $C_{13}H_{17}F_2NO_2$ requires: C, 60·7; H, 6·66; N, 5·45; F, 14·8%).

No crystalline product was isolated when HCl aq was used for the hydrolysis of the ester. The use of other reaction conditions for the displacement of toluenesulfonyloxy by fluorine was unsatisfactory. A number of attempts to replace the chlorine on *m*-[bis(2-chloroethyl)amino]hydrocinnamic acid and the methyl ester were also unsuccessful or incomplete with KF, AgF, SbF_3 in several solvents (N,N-dimethylformamide, acetonitrile, methyl Cellosolve, ethanol and diglyme).

m-Morpholinohydrocinnamic acid (XXI). A mixture of 4·34 g (7·53 mmoles) of XVII and 2·20 g (38·0 mmoles) KF in 20 ml dry N,N-dimethylformamide was stirred and heated at reflux temp for 22 hr, then worked up and hydrolyzed by the procedure used for XX, to obtain 0·58 g (33%) *m*-morpholinohydrocinnamic acid, m.p. 125–128°. Recrystallization from absolute ethanol gave the analytical sample, m.p. 137–137·5°; $\lambda_{max(\mu)}^{Nujol}$ 3·6–4·2 (COOH), 5·76 (C=O of CO_2H), 8·49 (C—O—C); it had R_f 0·40 in solvent B. (Found: C, 66·2; H, 7·32; N,5·76; and no fluorine. $C_{13}H_{17}NO_3$ requires: C, 66·3; H, 7·30; N, 5·95%).

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[20] W. A. Skinner, M. G. M. Schelstraete and B. R. Baker, *J. Org. Chem.* **26**, 1554 (1961).