(m, 2 H), 6.10 (m, 2 H), and 6.50 ppm (t, 2 H). The structure of the 1-bromocyclohepta-3,5-diene (XIV) was assigned on the basis of its nmr proton absorptions in the mixture of the two bromide products (CCl_4): δ 2.94 (m, 4 H), 4.38 (m, 1 H, CHBr), and 5.80 ppm (m, 4 H, vinylic). Similarly, the structure of the 1-bromomethylcyclohexa-2,4-diene (XV) was assigned on the basis of its nmr proton absorptions (CCl_4): δ 2.38 (m, 3 H), 3.30 (d, 2 H, J = 6.5 Hz, CH_2Br), and 5.80 ppm (m, 4 H, vinylic). The distilled bromide mixture had uv max (absolute $(C_2H_5)_2O$), 245 mμ (ϵ 5500); mass spectrum (70 eV), *m/e* 172 and 174 (molecule ion), 93, 91, 79, and 77. *Anal.* Calcd for C_7H_9Br: C, 48.55; H, 5.20; Br, 46.24. Found: C, 48.42; H, 5.09; Br, 46.49.

Using the information from the above product separation procedures, it was then possible to determine, by nmr analysis, the composition of the original bromination mixture. It was found that 69% of the bicyclo[4.1.0]hept-3-ene had reacted to give 53% 1-bromocyclohepta-3,5-diene (XIV), 13% 1-bromomethylcyclohexa-2,4-diene (XV), and 22% tropilidine. In a similar run with 1.00 g (10.7 mmol) of bicyclo[4.1.0]hept-3-ene and 1.93 g (10.8 mmol) of NBS in 20 ml of carbon tetrachloride solvent, 70% of the bicyclo[4.1.0]hept-3-ene reacted to give 54% XIV, 13% XV, and 20% tropilidine.

Registry No.—N-Bromosuccinimide, 128-08-5; III, 18933-49-8; β-bromopropionyl isocyanate, 18926-24-4; V, 18944-78-0; VI, 18933-48-7; VII, 18926-25-5; X, 18926-26-6; XI, 7515-41-5; XII, 18944-79-1; XIII, 18933-51-2; tropilidene, 544-25-2; XIV, 18926-29-9; XV, 18926-28-8.

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New Reactions of Polyfluoroaromatic Compounds. Pentafluorophenylalanine and Tetrafluorotyrosine

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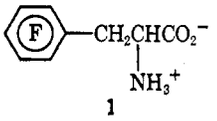
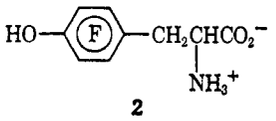
The reaction of α-bromo-β-pentafluorophenylpropionic acid (**4**) with ammonia gives *trans*-4-amino-2,3,5,6-tetrafluorocinnamic acid (**5**), rather than pentafluorophenylalanine (**1**). Compound **1** is prepared by hydrogenolysis of α-azido-β-pentafluorophenylpropionic acid, by reductive hydrolysis of the azlactone precursor, and by the acetamidomalonate procedure (the method of choice). Tetrafluorotyrosine (**2**) is prepared in 17% over-all yield from hexafluorobenzene by the latter method. The influence of polyfluoroaryl substitution on the acidity of the functional groups in these aromatic amino acids has been determined. The biological activity of **1** and **2** is discussed.

In two recent communications we reported the syntheses of *dl*-β-pentafluorophenylalanine[1] (**1**) and *dl*-tetrafluorotyrosine[2] (**2**). In the present paper we wish to discuss in detail the chemistry of these highly fluorinated α-amino acids and a number of related reactions of synthetic and mechanistic interest.



1



2

In our studies directed toward the synthesis of pentafluorophenylalanine, we approached this problem *via* the Meerwein arylation route. The application of this procedure to the preparation of amino acids has been reported by us[3] and others.[4]

The starting material for the synthesis was pentafluoroaniline (**3**), obtained in 86% yield by reaction of hexafluorobenzene with aqueous ammonia in a rocking-type autoclave at 170° for 24 hr. This was a substantial improvement over the yield reported previously.[5] A mixture of **3** and 48% hydrobromic acid, dissolved in acetone, was diazotized at 0–5° and added to acrylic acid in the presence of a catalytic amount of freshly purified copper(I) bromide to give 18% yield of α-bromo-β-pentafluorophenylpropionic acid (**4**). Attempted ammonolysis of **4**, by treating an ethanolic solution with liquid ammonia in a sealed tube for 4 days at room temperature, gave **5** in 91% yield. Compound **5** was soluble in aqueous alkali and did not form a hydrochloride. It absorbed bromine very slowly, but reacted rapidly with neutral potassium permanganate. A ninhydrin test was negative.

The infrared spectrum of **5** revealed two sharp bands at 3520 and 3415 cm^{-1}, broad weak absorption between 3100 and 2500 cm^{-1}, and a strong band at 1690 cm^{-1}. All of these observations suggested that **5** was an aminocinnamic acid. Comparison of its ultraviolet spectrum with those of related cinnamic acids[6,7] (Table I) provided strong evidence that this compound was *trans*-4-amino-2,3,5,6-tetrafluorocinnamic acid. Substitution of an amino group in the *para* position of *trans*-cinnamic acid causes a bathochromic shift of 67 mμ. Compound **5** shows a comparable shift of 68 mμ when compared with pentafluorocinnamic acid. The assignment is also consistent with previous observations that nucleophiles attack most substituted pentafluorophenyl compounds preferentially in the

(1) R. Filler and W. Gustowski, *Nature*, **205**, 1105 (1965).

(2) R. Filler and H. H. Kang, *Chem. Commun.*, 626 (1965).

(3) (a) R. Filler and H. Novar, *Chem. Ind.* (London), 468 (1960); (b) R. Filler, L. Gorelic, and B. Taqui-Khan, *Proc. Chem. Soc.*, 117 (1962); (c) R. Filler, A. B. White, B. Taqui-Khan, and L. Gorelic, *Can. J. Chem.*, **45**, 329 (1967).

(4) (a) G. H. Cleland, *J. Org. Chem.*, **26**, 3362 (1961); (b) A. M. Yurkevich, A. V. Dombrovskii, and A. P. Terent'ev, *J. Gen. Chem.* USSR, **28**, 226 (1958).

(5) G. M. Brooke, J. Burdon, M. Stacey, and J. C. Tatlow, *J. Chem. Soc.*, 1768 (1960).

(6) A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," 2nd ed, E. Arnold, London, 1957, p 269.

(7) A. K. Barbour, M. W. Buxton, P. L. Coe, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 808 (1961).

TABLE I

ULTRAVIOLET SPECTRA OF CINNAMIC ACIDS

Compound	λ_{max}^{EtOH}, mμ	ϵ_{max}
Cinnamic acid[a]		
cis	264	9,500
trans	273	21,000
trans-Pentafluorocinnamic acid[b]	257	42,000
trans-2-Fluorocinnamic acid	267.5	13,040
	214	8,300
trans-4-Aminocinnamic acid	340	27,000
	235	9,030
trans-4-Amino-2,3,5,6-tetrafluoro-cinnamic acid (**5**)	325	17,600
	230	8,800

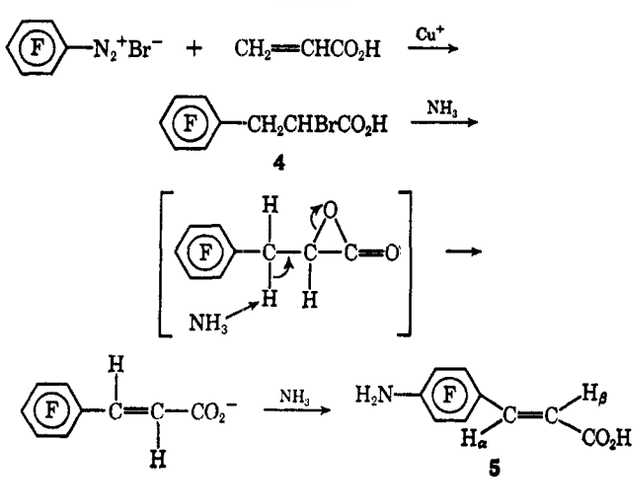
[a] See ref 6. [b] See ref 7.

para position.[8] The intensity of the absorption at 325 mμ favors the *trans* configuration.

The proton magnetic resonance spectra of **5** and of *trans*-4-aminocinnamic acid were determined in trifluoroacetic acid. The former shows a pair of doublets centered at δ 8.09 (J_{H_α,H_β} = 15 Hz) and 6.96 (J_{H_α,H_β} = 15 Hz), while the latter also exhibits a pair of doublets at δ 8.09 (J = 15 Hz) and 6.71 (J = 15 Hz). These values agree well with those observed for *trans*-cinnamic acid.[9] Compound **5** was also isolated in crude form when the reaction with ammonia was stopped after 15 hr. The ultraviolet spectrum of this material indicated contamination by a substance (λ_{max} 253 mμ), believed to be pentafluorocinnamic acid.[7]

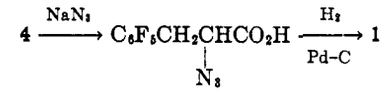
The reaction probably proceeds as shown in Scheme I.

SCHEME I



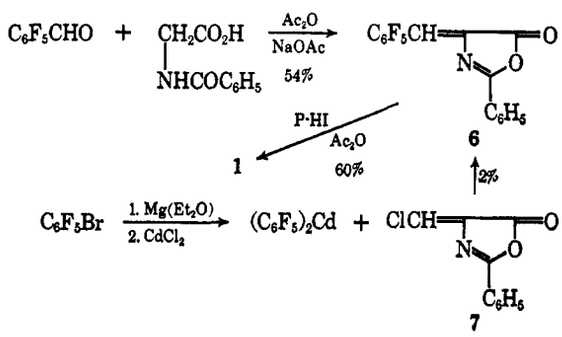
The action of ammonia on **4** leads to an incipient α-lactone.[10] Nucleophilic attack by ammonia at the α-carbon would then give the amino acid. However, if the β-hydrogens are unusually acidic, as in this case (owing to the electron-attracting inductive effect of the C_6F_5 group),[11] abstraction of a β-proton by strong base leads to elimination, which may occur to the exclusion of the displacement reaction. A similar behavior has been reported in the reaction of ammonia on ethyl 2-bromo-4,4,4-trifluorobutyrate.[12] Although the elimination is depicted as a concerted process, it is also possible that a carbanion mechanism (E1cb) is involved.

When, however, the bromo acid **4** was treated with azide ion,[12] a good nucleophile but a much weaker base than ammonia, displacement of halogen occurred to give the α-azido acid, which was converted to **1** on hydrogenolysis. Although the yields in the last two steps were good, we experienced difficulty in freeing small amounts of inorganic impurities from the amino acid.



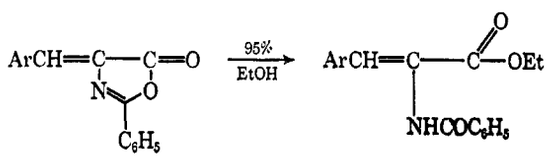
The synthesis of **1** was also accomplished by reductive hydrolysis of the azlactone, 2-phenyl-4-pentafluorobenzylidene-5(4H)-oxazolone (**6**)[13,14] (Scheme II).

SCHEME II



Compound **6** was prepared by the conventional Erlenmeyer procedure or in poor conversion (2%) by reaction of bis(pentafluorophenyl)cadmium with 2-phenyl-4-chloromethylene-5(4H)-oxazolone (**7**). The hydrogen analog of **6** has been prepared in good yield by the latter method.[15]

The strong electron attraction of the pentafluorophenyl group increases the susceptibility of the lactone carbonyl of **6** to nucleophilic attack and was manifested by the enhanced rate of uncatalyzed ethanolysis of the oxazolone ring. Reaction was followed spectrophotometrically by observing the rate of disappearance of the 310-mμ band. After 30 min, 60% reaction had occurred and, after 6 hr, ring opening was essentially complete. The hydrogen analog of **6** required 3–4 days for complete reaction.[16]



The method of choice for the synthesis of **1** was the acidic hydrolysis and decarboxylation of the substituted

(8) (a) J. C. Tatlow, *Endeavour*, **22**, 89 (1963); (b) J. Burdon, W. B. Hollyhead, and J. C. Tatlow, *J. Chem. Soc.*, 5152 (1965); (c) K. C. Ho and J. Miller, *Aust. J. Chem.*, **19**, 423 (1966).

(9) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," No. 1, Varian Associates, Palo Alto, Calif., 1962.

(10) E. Grunwald and S. Winstein, *J. Am. Chem. Soc.*, **70**, 841 (1948).

(11) R. Filler and C. S. Wang, *Chem. Commun.*, 287 (1968).

(12) H. M. Walborsky, M. Baum, and D. F. Loncrini *J. Amer. Chem. Soc.*, **77**, 3637 (1955); D. F. Loncrini and H. M. Walborsky, *J. Med. Chem.*, **7**, 369 (1964).

(13) G. W. Shishkin and W. P. Mamajev [*Izv. Akad. Nauk. SSSR, Ser. Khim.*, 934 (1965)] reported the synthesis of **1** in 77% yield by a two-step reductive hydrolysis of **6**.

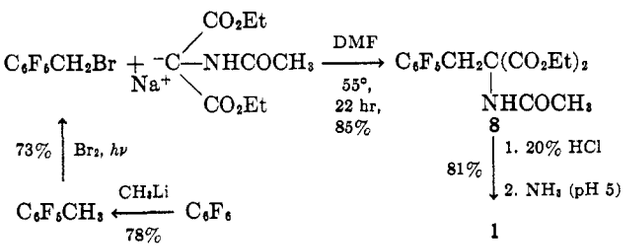
(14) Dr. P. L. Coe, University of Birmingham, Birmingham, England, obtained an impure sample of **1** by this route (private communication).

(15) H. Behringer and H. Taul, *Chem. Ber.*, **90**, 1398 (1957).

(16) R. Filler and H. Novar, *J. Org. Chem.*, **25**, 663 (1960).

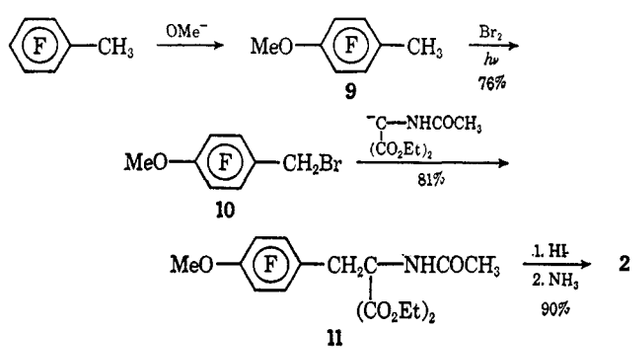
ester **8**, prepared from pentafluorobenzyl bromide and diethyl sodioacetamidomalonate (Scheme III). The

SCHEME III



success of this method led us to employ the same approach for the synthesis of *dl*-tetrafluorotyrosine (**2**) (Scheme IV). Pentafluorotoluene reacted with sodium

SCHEME IV



methoxide in refluxing methanol to yield 4-methyl-2,3,5,6-tetrafluoroanisole (**9**) in 45% conversion. Bromination of **9** furnished the corresponding benzyl bromide (**10**), which was converted to the adduct **11**. Demethylation of the methoxy group, hydrolysis of the amide and ester linkages, and decarboxylation were effected in one step by heating a mixture of **11** and 50% HI under reflux for 3 days to give the amino acid **2** in 90% yield, after careful treatment with ammonia (to pH 5). The over-all yield of tetrafluorotyrosine starting from hexafluorobenzene was 17%.

Tetrafluorotyrosine gives a positive ninhydrin test (as does pentafluorophenylalanine), a positive ferric chloride test for a phenolic hydroxyl group, and a positive Millon reaction, characteristic of tyrosine. Its infrared spectrum is consistent with its structure and the ultraviolet spectrum in 0.1 *N* HCl exhibits a shoulder at 256 mμ, which undergoes a bathochromic shift to 280 mμ at pH 5.4 (*vide infra*) due to formation of the substituted phenoxide ion.

The influence of polyfluoroaryl substitution on the acidity of the functional groups in these aromatic amino acids was determined by potentiometric titration. The pK_a values obtained by this method were compared with those for their nonfluorinated analogs, and the results are summarized in Table II.

It is apparent that the electron-attracting effect of the polyfluoroaryl groups exerts no detectable influence on the acidity of the carboxyl function. However, the acidity of the NH_3^+ group is increased in both **1** and **2** by almost 1 pK unit. It seems likely that an inductive field effect is operative. The observation that the phenolic OH in **2** is 10^5 times more acidic than in tyrosine reflects the strong electron attraction of the four

TABLE II

EFFECT OF POLYFLUOROARYL SUBSTITUTION ON pK_a's OF AROMATIC AMINO ACIDS AT 24°

Compound	pK(CO_2H)	pK(OH)	pK(NH_3^+)
$C_6H_5CH_2CHCO_2H$ (NH2)	2.16[a]	...	9.12[a]
$C_6F_5CH_2CHCO_2H$ (NH2)	2.2	...	8.3
p-$HOC_6H_4CH_2CHCO_2H$ (NH2)	2.20[b]	10.43[b]	9.19[b]
p-$HOC_6F_4CH_2CHCO_2H$ (NH2)	2.2	5.4[c]	8.3

[a] E. L. Bennett and C. Niemann, *J. Am. Chem. Soc.*, **72**, 1804 (1950). [b] A. Albert, *Biochem. J.*, **50**, 690 (1952). [c] Confirmed independently by ultraviolet spectrophotometric determination (see discussion).

nuclear fluorine atoms when the ionizing group is attached directly to the ring. A similar effect has been found for pentafluorophenol [pK 5.3[17] (5.5)[18]].

Both *dl*-pentafluorophenylalanine and *dl*-tetrafluorotyrosine have been examined for biological activity. The compounds produced no obvious symptoms in mice at doses up to 1000 mg/kg ip, nor did they alter citric acid levels in mouse kidney or brain at 178 mg/kg ip.[19] Tetrafluorotyrosine has been found to be a weak inhibitor of tyrosine hydroxylase.[20] It also failed to show transport against a concentration gradient by the *in vitro* small intestine of the hamster.[21] This is consistent with the net negative charge carried by the molecule at pH 7.4 (due to ionization of the phenolic OH).

Experimental Section[22]

2,3,4,5,6-Pentafluorotoluene was prepared from hexafluorobenzene and methyllithium according to a procedure described previously.[7] A 60% yield of product, bp 115–118°, was obtained.

4-Methyl-2,3,5,6-tetrafluoroanisole.—Pentafluorotoluene (33.7 g, 0.185 mol) was added to 250 ml of dry methanol containing sodium methoxide prepared from 4.26 g (0.185 g-atom) of sodium, and the mixture was heated under reflux for 18 hr. The solution was cooled and poured into 2 l. of cold water. After the aqueous solution was extracted with three 200-ml portions of ether, the combined organic layer was dried over anhydrous magnesium sulfate, filtered, and distilled through a column (3 in.), packed with glass helices, to obtain 16 g (45%) of product, bp 165–169°. A proton magnetic resonance spectrum of the product as the neat liquid showed a triplet (δ 2.16, $J_{H,F}$ = 2.2 Hz), assigned to the methyl protons, and another triplet (δ 4.03, $J_{H,F}$ = 1.2 Hz), for the methoxy protons.

4-Methoxy-2,3,5,6-tetrafluorobenzyl Bromide.—Bromine (12.5 g, 0.078 mole) was added dropwise to 15 g (0.0773 mole) of 4-methyl-2,3,5,6-tetrafluoroanisole in 125 ml of carbon tetrachloride while the reaction mixture was being illuminated and heated under reflux by a closely located 200-W light bulb. The solution turned light brown after 4 hr of irradiation and refluxing,

(17) E. J. Forbes, R. D. Richardson, M. Stacey, and J. C. Tatlow, *J. Chem. Soc.*, 2019 (1959).
(18) J. M. Birchall and R. N. Haszeldine, *ibid.*, 3653 (1959).
(19) A. Weissman and B. K. Koe, *J. Pharmacol. Exp. Ther.*, **155**, 135 (1967).
(20) M. Levitt, private communication.
(21) R. P. Spencer, private communication.
(22) Melting points and boiling points are uncorrected.

indicating the completion of bromination. Most of the solvent was distilled through a 3-in. column packed with glass helices, and the remaining liquid was distilled *in vacuo* to collect 16 g (76%) of product, boiling range 96–102° (5 torr). The product was a strong lachrimator and turned light brown after several weeks of storage. A proton magnetic resonance spectrum of this compound as the neat liquid showed a triplet (δ 4.16, $J_{H,F}$ = 1.5 Hz), assigned to the methoxy protons, and another triplet (δ 4.54, $J_{H,F}$ = 1.3 Hz), assigned to the benzylic protons.

Diethyl Sodioacetamidomalonate.—Sodium ethoxide solution, prepared from 3.13 g (0.115 g-atom) of sodium added to 50 ml of dry ethanol, was mixed with 25 g (0.109 mol) of diethyl acetamidomalonate in 250 ml of ethanol. The combined solution was refluxed for 4 hr, and then approximately 200 ml of solvent was removed by evaporation *in vacuo*. To the resulting syrupy liquid was added 250 ml of ether to precipitate diethyl sodioacetamidomalonate. The pale yellow solid was collected by filtration, to give 25 g of product (92%).

Diethyl 4-Methoxy-2,3,5,6-tetrafluorobenzylacetamidomalonate.—4-Methoxy-2,3,5,6-tetrafluorobenzyl bromide (16 g, 0.057 mole), 16 g (0.638 mole) of diethyl sodioacetamidomalonate, and 175 ml of dry dimethylformamide were mixed and heated at 55° for 22 hr while the heterogeneous mixture was being stirred. The reaction mixture was poured into 750 ml of cold water, and the resulting white solid was collected by filtration. The crude product was washed several times with water and dried in a vacuum desiccator, to give 19 g (81%) of a white solid, with a wide melting range around 140°. The melting point was raised to 148–149° after three recrystallizations from 80% ethanol (needles). *Anal.* Calcd for $C_{17}H_{19}O_5NF_4$: C, 49.85; H, 4.67. Found: C, 49.92; H, 4.74. The proton magnetic resonance spectrum showed a triplet (δ 1.30, J = 7.4 Hz) and a quadruplet (δ 4.28, J = 7.4 Hz) for CH_3 and CH_2 protons of $CO_2CH_2CH_3$ groups, a singlet (δ 2.0) for $COCH_3$ group, a broad singlet (δ 6.65) for the NH group, a triplet (δ 3.75, $J_{H,F}$ = 1.2 Hz) for the benzylic protons, and another triplet (δ 4.99, $J_{H,F}$ = 1.3 Hz) for the methoxy protons.

***dl*-2,3,5,6-Tetrafluorotyrosine.**—A heterogeneous mixture of 15 g (0.0867 mole) of 4-methoxy-2,3,5,6-tetrafluorobenzyldiethylacetamidomalonate and 80 ml of 50% hydriodic acid was vigorously refluxed for 3 days. The resulting clear solution was then subjected to vacuum distillation to remove volatile components. The remaining viscous residue was dissolved in a minimum amount (8 ml) of water and filtered to remove insoluble materials. When the filtrate was neutralized with concentrated ammonium hydroxide solution to approximately pH 5.5, a large quantity of white solid appeared. The solid product was thoroughly washed with water, ethanol, and finally, with ether, and dried to yield 8.3 g (90%) of amino acid. Crystallization from hot water gave granular crystals. Upon rapid heating, the amino acid turned brown at 270° and turned to a black liquid at 275°. *Anal.* Calcd for $C_9H_7O_3NF_4$: C, 42.69; H, 2.78; N, 5.53. Found: C, 42.28; H, 2.92; N, 5.15. The infrared spectrum of the free amino acid as a potassium bromide disk showed unresolved broad bands between 3280 and 2310 cm^{-1}, attributable to the phenolic hydroxyl and the ammonium groups. The band at 1610 cm^{-1} was assigned to the asymmetric bending of ammonium ion and the one at 1575 cm^{-1} to the asymmetric stretching vibrations of carboxylate ion. The potentiometric titration of three acidic functions of tetrafluorotyrosine revealed pK(COOH) = 2.2, pK(OH) = 5.4, and $pK(NH_3^+)$ = 8.3. The ultraviolet spectrum of the amino acid in 0.1 *N* hydrochloric acid showed a shoulder at 256 mμ (ϵ 412). A bathochromic shift to 275 mμ due to phenoxide ion was observed in 0.1 *N* sodium hydroxide solution. Calculation[23] from the ultraviolet spectral data gave pK(OH) = 5.37. The amino acid gave a positive ninhydrin test, a positive ferric chloride test for a phenolic hydroxyl group, and a positive Millon test, characteristic of tyrosine. Ascending paper chromatography was carried out in water-saturated phenol according to the procedure of Consden, *et al.*[24] Alcoholic solutions of ninhydrin and pyridine were used as developing reagents. Tetrafluorotyrosine gave a purple spot with R_f 3.64, and tyrosine showed a purple color with R_f 6.35.

(23) F. L. J. Sixma and H. Wynberg, "A Manual of Physical Methods in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1964, p 257.

(24) R. Consden, A. H. Gordon, and A. J. P. Martin, *Biochem., J.*, **38**, 224 (1944).

2,3,4,5,6-Pentafluorobenzyl Bromide.—The reaction was carried out according to the procedure used for the bromination of 4-methoxy-2,3,5,6-tetrafluoroanisole. From 33.6 g (0.21 mol) of bromine and 36.4 g (0.20 mol) of pentafluorotoluene, 39 g of pentafluorobenzyl bromide (75%) was obtained, bp 173–177° (lit.[7] bp 174–175°).

Diethyl 2,3,4,5,6-Pentafluorobenzylacetamidomalonate.—The method described previously for the preparation of diethyl 4-methoxy-2,3,5,6-tetrafluorobenzylacetamidomalonate was followed. From 10.5 g (0.0403 mol) of pentafluorobenzyl bromide and 11.7 g (0.0465 mol) of diethyl sodioacetamidomalonate, after 22 hr of reaction at 55° in 125 ml of dimethylformamide, was obtained 14 g (85%) of product, mp 124–126°.

***dl*-2,3,4,5,6-Pentafluorophenylalanine.**—A mixture of 11 g (0.0275 mol) of diethyl pentafluorobenzylacetamidomalonate and 200 ml of 20% hydrochloric acid was refluxed for 20 hr. Most of the liquid was then removed by use of a rotating vacuum evaporator. The viscous liquid residue was dissolved in 5 ml of water and treated with concentrated ammonium hydroxide solution so that the pH was approximately 5.5 to indicator paper. The white solid formed during the neutralization was collected by filtration and thoroughly washed with water and alcohol to give 5.7 g (81%) of *dl*-pentafluorophenylalanine, mp 253–255° dec. *Anal.* Calcd for $C_9H_6O_2NF_5$: C, 42.36; H, 2.37; N, 5.49. Found: C, 41.98; H, 2.63; N, 5.77. Potentiometric titration revealed pK(COOH) = 2.2 and $pK(NH_3^+)$ = 8.3. Paper chromatography was carried out by employing the method used for tetrafluorotyrosine. Pentafluorophenylalanine gave a blue spot with R_f 8.35 while phenylalanine revealed a purple spot with R_f 8.75. The infrared spectrum of the amino acid hydrochloride as a KBr disk exhibited bands at 3115 (m) (NH_3^+), broad absorption in the range 3100–2500 (CH_2, CH, and CO_2H), and 1735 (s) (CO_2H) cm^{-1}.

Pentafluoroaniline, bp 157–159°, was prepared in 86% yield by reaction of hexafluorobenzene with aqueous ammonia in a rocking-type autoclave at 167° for 24 hr. This was a substantial improvement over the yield reported previously.[5]

2-Bromo-3-pentafluorophenylpropionic Acid (4).—Pentafluoroaniline (7.5 g) was dissolved in 20 ml of acetone and 12 ml of 48% hydrobromic acid. The mixture was placed in a three-necked flask and fitted with a mechanical stirrer and thermometer. The flask was swept with nitrogen and cooled to 0–2° with an ice–water bath. A solution containing 6 g of acrylic acid, 0.2 g of cuprous bromide, and 20 ml of acetone was added dropwise. During 30 min, a solution of 2.8 g of sodium nitrite in 8 ml of water was added, the temperature being maintained at 0–5°. The yellow-brown mixture was stirred for an additional 1 hr at 0–5° and for 3 hr as the temperature rose to 30°. The mixture was poured over 100 g of crushed ice and the orange oil which separated was taken up in ether. The remaining aqueous solution was extracted three times with ether and the combined ether extracts were dried overnight over anhydrous magnesium sulfate. After removal of the ether, the residue was dissolved in 50 ml of benzene and 10 ml of ethanol and the solution was placed in a bath of Dry Ice–acetone. The solid which precipitated was removed by filtration at −20° and shown to be unreacted acrylic acid. The filtrate was evaporated to dryness and 20 ml of chloroform was added. After cooling at −65° for 24 hr, a colorless solid, mp 138–145°, separated. After crystallization from chloroform, 2.4 g (18%) of 2-bromo-3-pentafluorophenylpropionic acid, mp 146–148°, was obtained. *Anal.* Calcd for $C_9H_4O_2F_5Br$: C, 33.9; H, 1.25; mol wt, 319. Found: C, 34.5; H, 1.40; mol wt (neut equiv), 319. The infrared spectrum showed a broad band at 2985–2550 (carboxyl OH), strong absorption at 1710 (acid C=O), strong bands at 1515 and 1493 (aromatic ring), and a series of intense bands between 1420 and 930 cm^{-1} (C–F stretching).

2-Azido-3-pentafluorophenylpropionic Acid.—2-Bromo-3-pentafluorophenylpropionic acid (0.9 g) and 0.9 g of sodium azide were dissolved in 5 ml of water and 20 ml of ethanol, the solution was cooled in an ice bath, and 50 ml of ether was added. The precipitate which formed was removed by filtration and the ether layer of the filtrate was dried over anhydrous magnesium sulfate and evaporated to dryness. The residue was collected and used in the next step without further purification. The infrared spectrum of this material (as a KBr disk) showed absorption at 2120 cm^{-1} (s), characteristic of the azido group.

***dl*-Pentafluorophenylalanine.**—Crude 2-azido-3-pentafluorophenylpropionic acid (0.8 g) was dissolved in 30 ml of ethanol,

and 0.5 g of palladium-on-charcoal (10%) catalyst was added. Reduction was carried out in a Parr hydrogenator at room temperature during 24 hr. The catalyst was removed by filtration and the filtrate was concentrated to give 0.75 g of solid residue, which was washed with chloroform and crystallized from ethanol. The resulting material, melting range 223–240° dec, showed traces of inorganic impurity but could not be readily purified further. This material gave a strong positive ninhydrin reaction. Its infrared spectrum was essentially identical with that of the *dl*-pentafluorophenylalanine prepared *via* the acetamidomalonic ester route. The azide band was absent.

Reaction of 4 with Ammonia.—In a 100-ml Pyrex tube sealed at one end was placed 3.75 g of bromo acid dissolved in 10 ml of ethanol. The solution was cooled to −70° and 35 ml of liquid ammonia was added. The tube was sealed and shaken at room temperature for 4 days. The tube was opened and the excess ammonia was driven off by air blowing. Ethanol was removed by heating on a steam bath to give a solid residue. After crystallization from 66% ethanol, 2.5 g of white needles, mp 192°, was obtained. This material failed to give a ninhydrin reaction, was soluble in aqueous Na_2CO_3 and NaOH, but was insoluble in dilute HCl. This product reacted slowly with bromine in CCl_4, but decolorized an aqueous solution of $KMnO_4$; spectral data: ir, 3520 and 3415 (NH_2), 3100–2500 (CO_2H), 1690 (conjugated CO_2H) cm^{-1}; ultraviolet, λ 325 mμ (ϵ 17,600) and 230 mμ (ϵ 8800); pmr, δ 8.09 (doublet, $J_{H,H}$ = 15 Hz), 6.96 (doublet, $J_{H,H}$ = 15 Hz.). *Anal.* Calcd for $C_9H_5O_2NF_4$: C, 45.96; H, 2.13; N, 5.96; F, 32.34; mol wt, 235. Found: C, 46.29; H, 2.14; N, 6.67; F, 32.46; mol wt (neut equiv), 232. The yield of 4-amino-2,3,5,6-tetrafluoro-*trans*-cinnamic acid was 91%.

2-Phenyl-4-pentafluorobenzylidene-5(4H)-oxazolone. Method A.—Pentafluorobenzaldehyde reacted with hippuric acid in the presence of sodium acetate and acetic anhydride according to a known procedure.[25] The yield of light yellow needles, mp 169.5–170.2°, was 54%; spectral data: ir, 3080, 1804 (vs) (lactone C=O), 1666, 1645, 1600, 1560, 1450, 1330, 1068, 992, 700 cm^{-1}; ultraviolet, $\lambda_{max}^{Et_2O}$ 310 mμ (ϵ 28,550), 254 (ϵ 14,800), 237 (ϵ 15,240), $\lambda_{max}^{CHCl_3}$ 320 mμ. In 95% ethanol solution,[16] diminution of the band at 310 mμ occurs after less than 30 min with a corresponding development and increase in intensity of a new band at 230 mμ. *Anal.* Calcd for $C_{16}H_6O_2NF_5$: C, 56.64; H, 1.78. Found: C, 56.25; H, 1.84.

Method B.—Pentafluorobromobenzene (3.1 g) in 15 ml of anhydrous ether was added to 0.313 g of magnesium turnings in a three-neck flask, fitted with a mechanical stirrer, reflux condenser, and dropping funnel. After the Grignard reagent had formed, an additional 15 ml of ether was added, the contents of the flask were cooled, 1.15 g of cadmium chloride was added in two portions, and the mixture was stirred and warmed slightly for 30 min. Ether was removed under diminished pressure and replaced by 15 ml of thiophene-free benzene. A solution of 2.5 g of 2-phenyl-4-chloromethylene-5(4H)-oxazolone[15] in 20 ml of benzene was added with continuous stirring during 10–15 min. The yellow reaction mixture was warmed on a water bath for 1.5 hr (50–60°), cooled, and acidified with dilute acetic acid. The benzene layer was separated and dried over anhydrous magnesium sulfate, and the benzene was removed to leave about 100 mg (*ca* 2%) of azlactone, mp 170–172°. This material was identical with that obtained by method A.

***dl*-Pentafluorophenylalanine.**—When a mixture of the aforementioned oxazolone and red phosphorus in acetic anhydride was gently refluxed with 50% hydriodic acid for 3–4 hr,[25] a 60% yield of amino acid, mp 251–254° dec, was obtained. This material was identical with that obtained by the acetamidomalonate method (*vide supra*).

Registry No.—**1**, 3321-96-8; **2**, 18933-45-4; **4**, 18926-19-7; **5**, 18933-46-5; **6**, 2865-08-9; **8**, 18944-76-8; **9**, 3150-40-1; **10**, 4910-40-1; **11**, 4910-41-2; **2-fluoro-*trans*-cinnamic acid**, 18944-77-9; **4-amino-*trans*-cinnamic acid**, 17570-30-8.

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Condensed Cyclobutane Aromatic Compounds. XXX. The Synthesis of Some Unusual 2, 3-Naphthoquinonoid Heterocycles. A Synthetic Route to Derivatives of Naphtho[2, 3-*b*]biphenylene and Anthra[*b*]cyclobutene[1]

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The isolable, but highly reactive, 1,3-diphenylnaphtho[2,3-*c*]furan (**9**) has been prepared by a simple reaction sequence starting with 2,3-dimethylnaphthalene. Compound **9**, which represents the first known stable 2,3-naphthoquinonoid substance, is an extremely reactive diene component in the Diels–Alder reaction: its reactivity exceeds that of its much studied lower benzolog, 1,3-diphenylbenzo[*c*]furan (**7**). A number of Diels–Alder adducts of **9** have been prepared, some of which have been aromatized; in this way, the synthesis of derivatives (**36** and **47**) of the naphtho[2,3-*b*]biphenylene and anthra[*b*]cyclobutene systems has been achieved. Reaction of **9** with phosphorus pentasulfide gives 1,3-diphenylnaphtho[2,3-*c*]thiophene (**10**), the first derivative of a new aromatic heterocyclic system. Thiophene **10** is a much less reactive diene in Diels–Alder additions than is furan **9**, suggesting considerable resonance stabilization for the naphtho[2,3-*c*]thiophene system.

In the course of studies concerned with synthetic routes to benzocyclobutene (**1**) and naphtho[*b*]cyclobutene (**2**), our attention became drawn to differences in reactivity between their ring-opened *o*-quinonoid hydrocarbon precursors **3** and **4**. Although both **3** and **4** are extremely reactive and nonisolable species, the 2,3-naphthoquinonoid compound **4** shows evidence of being the more reactive of the two. This difference in behavior is not unexpected if **3** and **4** are viewed as carbon analogs of *o*-benzoquinone (**5**) and the as yet unknown 2,3-naphthoquinone (**6**), respectively.[3] The *o*-quinonoid system of **3** can achieve a fair degree of stabilization if the methylene groups form part of a heterocyclic ring, and especially if they also bear conjugating substituents. Thus, 1,3-diphenylbenzo[*c*]furan (**7**) and 1,3-diphenylbenzo[*c*]thiophene (**8**)

(1) A portion of this work was reported as a preliminary communication: M. P. Cava and J. P. VanMeter, *J. Am. Chem. Soc.*, **84**, 2008 (1962).

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