Tetrafluorotyrosine: Synthesis and Properties

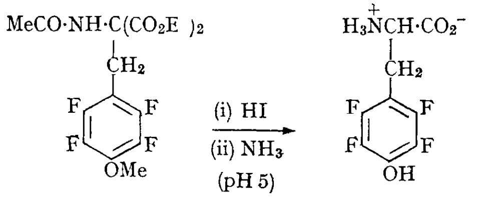
By R. FILLER and H. H. KANG

(*Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois,* 60616, *U.S.A.*)

IN a recent communication[1] we described the synthesis of the first polyfluorinated aromatic α-amino-acid, DL-pentafluorophenylalanine. We now report a convenient synthesis of 2,3,5,6-tetrafluorotyrosine (I) and some properties of this new aromatic amino-acid.

Pentafluorotoluene, prepared in 75% yield by reaction of hexafluorobenzene with methyl-lithium, reacted with sodium methoxide in refluxing methanol to give a 45% yield of 4-methyl-2,3,5,6-tetrafluoroanisole, boiling range 165—169°;[2] n.m.r. (60 Mc./sec., neat with tetramethylsilane as internal standard): $\delta = 2{\cdot}16$ p.p.m. downfield (triplet, $J_{\text{H-F}} = 2{\cdot}2$ c./sec., C–CH_3) and $\delta = 4{\cdot}03$ p.p.m. downfield (triplet, $J_{\text{H-F}} = 1{\cdot}2$ c./sec., O–CH_3).[3] This ether, on treatment with bromine in refluxing carbon tetrachloride, in the presence of light, was converted in 76% yield into 4-methoxy-2,3,5,6-tetrafluorobenzyl bromide, boiling range 95—102°/5 mm., a strong lachrymator. The bromide reacted with sodiodiethylacetamidomalonate in dimethylformamide at 55° during 22 hours to give an 81% yield of 4-methoxy-2,3,5,6-tetrafluorobenzyldiethylacetamidomalonate (II), m.p. 148—149°. A heterogeneous mixture of (II) and 50% hydroiodic acid was heated under reflux for three days to give a clear solution which, after work-up and addition of ammonia to pH 5, furnished compound (I), m.p. 271—272° dec., in 90% yield. The hydrolysis and ether cleavage were thus smoothly effected in a single step.

Tetrafluorotyrosine gives a positive ninhydrin test, a positive ferric chloride test for a phenolic hydroxyl group, and a positive Millon reaction, characteristic of tyrosine. The infrared spectrum of (I) is consistent with its structure and the ultraviolet spectrum in $0{\cdot}1$N-HCl reveals a shoulder at 256 mμ, which undergoes a bathochromic



(II) (I)

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[1] R. Filler and W. Gustowski, *Nature*, 1965, **205**, 1105.

[2] This material contains about 5—6% of the 2- and 3-methoxy-isomers (gas–liquid chromatography).

[3] J. Burdon, *Tetrahedron*, 1965, **21**, 1101. This author reported a chemical shift (δ) of $3{\cdot}98$ (triplet, $J = 1{\cdot}2$ c./sec.) for this compound in acetone solution, but details of this preparation have not been published.

shift to 280 mμ at pH 5·4, owing to formation of phenoxide ion. The three acidic functions in (I) were shown by potentiometric titration to be: pK(CO_2H) = 2·2, pK(OH) = 5·4 (confirmed independently by the ultraviolet spectral data), and pK(NH_3^+) = 8·3. Tyrosine exhibits pK's of 2·2, 10·0, and 9·1, respectively. The observation that the phenolic $^-$OH in (I) is nearly 10^5 times more acidic than in tyrosine reflects the powerful electron-attracting influence of the four fluorine atoms and is consistent with the pK of 5·3[4] (5·5)[5] observed for pentafluorophenol. The increased acidity of the NH_3^+ group, with no change for the CO_2H function, suggests that a conformational preference may permit the NH_3^+ group to interact with an *ortho*-fluorine atom across intramolecular space.

Tetrafluorotyrosine is presently being examined for possible biological activity.

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[4] E. J. Forbes, R. D. Richardson, M. Stacey, and J. C. Tatlow, *J. Chem. Soc.*, 1959, 2019.

[5] J. M. Birchall and R. N. Haszeldine, *J. Chem. Soc.*, 1959, 3653.