Acknowledgments. We very gratefully acknowledge the help of Professor R. B. Merrifield, who gave generously of his time in teaching one of us (A. R.) his synthesis technique. We are indebted also to Professor S. Sakakibara for communicating his results to us before publication, and to Professor G. P. Hess for lending us the HF vacuum line.

(15) A. B. Robinson and M. D. Kamen, *Proc. Natl. Acad. Sci. U. S.*, in press.
(16) Advanced Research Fellow, American Heart Association.
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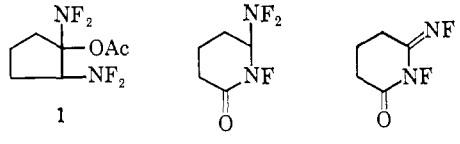
Rearrangements of Organic Fluoramines. Preparation of 3-Difluoramino-2-fluoro-2-azacyclohexanone and 3-Fluoro-3-(3-carbomethoxypropyl)diazirine

Sir:

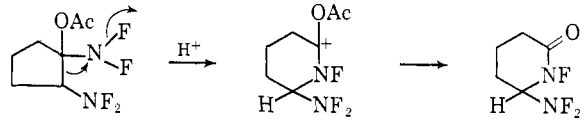
During a study of the properties of organic difluoramino compounds we prepared 1,2-bis(difluoramino)-1-acetoxycyclopentane (**1**), bp 42° (1 mm), mixture of *cis* and *trans* isomers by vpc and ^{19}F nmr (*Anal.* Found: C, 36.88; H, 4.69; N, 12.14; F, 33.4), from 1-acetoxycyclopentene and tetrafluorohydrazine.[1,2] Treatment of this bis(difluoramine) (**1**) with 96 or 100% sulfuric acid or with fluorosulfonic acid produced (60–70%) 3-difluoramino-2-fluoro-2-azacyclohexanone (**2**) as the only isolable organic product. Samples of **2** were purified by chromatography on silica gel. *Anal.* Found: C, 35.78, H, 4.46, N, 17.02, F, 33.6, infrared λ_{max} 5.75 (C=O) and 10.8–12 μ (NF). The ^{19}F nmr spectrum[3] of **2** was deceptively simple; two apparent quartets at −1428, −1444, −1460, −1476, and at +2268, +2284, +2304, +2320 cps were observed in CCl_4 solution. The proton spectrum exhibited an apparent quartet of multiplets centered at δ 5.29 ($HCNF_2$)[1] and a broad peak 100–170 cps downfield from TMS due to the trimethylene chain.[4] The timethylene chain is not attached to >NF since a shift of greater than 200 cps from TMS would be expected.[5]



1 **2** **3**

Further insight into the spectra of **2** was gained when ^{19}F homonuclear decoupling confirmed couplings of about 25 cps between the NF and NF_2 nuclei. That the >NF should appear as a quartet due to a coincidence of ^{1}H–^{19}F and ^{19}F–^{19}F couplings was now evident; however, the NF_2 group should only be a triplet. The only tenable hypothesis was that the NF_2, being on an asymmetric carbon, had nonequivalent fluorines only slightly shifted relative to one another. The nonregular splitting of the CH quartet and ^{19}F spectra run on solutions of trifluoroacetic acid confirmed the hypothesis. The familiar AB quartet of NF_2 on asymmetric carbon[1,5] was now apparent: each of the strong central resonances was a triplet from the fortuitously equal effects of proton and >NF couplings. Homo- and heteronuclear decoupling experiments on trifluoroacetic acid solutions confirmed all the assumptions made in the spectral interpretations of this deceptive ABMX system.

Formation of **2** from **1** can be rationalized as a rearrangement occurring with acid-catalyzed loss of fluoride ion from nitrogen.[6] Other routes from **1** to **2** are conceivable, of course.

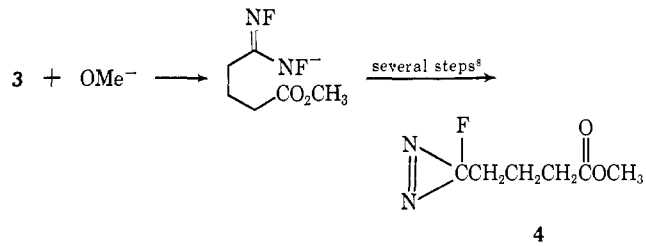


1 **2**

Dehydrofluorination of **2** with triethylamine in methylene chloride produced fluorimine **3** as a mixture of *syn* and *anti* isomers (*Anal.* Found: C, 40.52, H, 4.34, N, 18.11). The ^{19}F nmr spectrum of **3** consisted of peaks at ϕ −29.4 and +68.9 due, respectively, to the C=NF and the NF of the *anti* form, and of much weaker peaks at ϕ −18.9 (doublet, J_{FF} = 96 cps) and +61.9 (doublet, J_{FF} = 96 cps) due to the same functional groups in the *syn* isomer.

Treatment of either **2** or **3** with excess sodium methoxide in methanol produced 3-fluoro-3-(3-carbomethoxypropyl)diazirine (**4**); λ_{max} (cyclohexane) 358, 341 mμ (ϵ 234, 203), respectively.[7] *Anal.* Found: C, 45.10, H, 5.97, N, 17.22. The ^{19}F nmr spectrum of **4** had the C*F* peak at ϕ +139.2 (triplet, J_{HF} = 8 cps), and the infrared spectrum had an ester carbonyl absorption at 5.70 μ and the strong diazirine absorption at 6.39 μ.[7]

The mechanism for the formation of diazirine **4** undoubtedly involves cleavage of **3** to produce the intermediate shown; the steps involved in going from this intermediate to **4** are the same as formulated for the synthesis of 3-halodiazirines from amidines and sodium hypochlorite.[8]



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(1) R. C. Petry and J. P. Freeman, *J. Am. Chem. Soc.*, **83**, 3912 (1961); A. J. Dijkstra, J. A. Kerr, and A. F. Trotman-Dickenson, *J. Chem. Soc., Sect. A*, 582 (1966).
(2) The product mixture was about 41% *cis* and 59% *trans* by vpc. The second peak eluted was assigned the *cis*-difluoramino structure because it was reduced at more anodic potential, consistent with the results of an investigation of the reduction potential of related *cis* and *trans* isomers: K. J. Martin, unpublished studies.
(3) At 40 Mc with CCl_3F as internal standard; ϕ values are given in parts per million from internal CCl_3F.
(4) At 60 Mc, Varian A-60 spectrometer.
(5) See F. A. Johnson, C. Haney, and T. E. Stevens, *J. Org. Chem.*, in press, for a detailed discussion of the nmr spectra of 1,2-bis-(difluoramino)-1,2-diphenylethane.
(6) K. Baum and H. M. Nelson, *J. Am. Chem. Soc.*, **88**, 4459 (1966).
(7) For the characteristic spectra of diazirines see W. H. Graham, *ibid.*, **84**, 1063 (1962), and R. A. Mitsch, *J. Heterocyclic Chem.*, **1**, 59 (1964).
(8) W. H. Graham, *J. Am. Chem. Soc.*, **87**, 4396 (1965).

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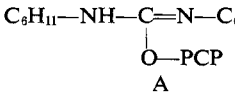
On the Optical Purity of Peptide Active Esters Prepared by N,N′-Dicyclohexylcarbodiimide and "Complexes" of N,N′-Dicyclohexylcarbodiimide–Pentachlorophenol and N,N′-Dicyclohexylcarbodiimide–Pentafluorophenol[1]

Sir:

In previous papers[2] we reported the use of active pentachlorophenyl esters for the synthesis of peptides and polypeptides. We report now the preparation of peptide-active PCPOH and PFPOH[3] esters in high optical purity and racemization studies of such esters using the Anderson[4] and Young[5] racemization tests. Active esters were prepared by (a) the backing-off procedure of Goodman,[6] (b) the "usual" method,[7] *i.e.*, from the N-protected peptides and phenol components, using N,N′-dicyclohexylcarbodiimide (DCC) as condensing agent,[8] (c) the "reverse" DCC procedure,[9] and (d) the use of a conveniently prepared crystalline "complex" consisting of the isourea derivative (A)



A

and two PCPOH. A similar structure can be assigned to the PFPOH "complex".[10] The optical purity of the peptide active esters obtained by procedures b, c, or d was determined by comparing their rotations to those of the pure compounds prepared by the backing-off procedure.[6] Remarkable is the high optical purity of the crude Z-Gly-Phe-OPCP and Z-Gly-Phe-OPFP, prepared either by the usual[11] and "reverse" methods or with the "complex," when compared with the low optical purity of the crude Z-Gly-Phe-ONP obtained by procedure b or c.[12] With the usual method at −10°, 90% optically pure Z-Gly-Phe-OPCP in 71% yield and 90 to 100% optically pure ester in 86 to 92% yield using the "complex" at room temperature[13] were obtained; similar results were obtained for the corresponding PFPOH esters. The effect of temperature and solvent has been emphasized in controlling racemization during peptide synthesis[14] and was found to be important in the preparation of active esters reported here. These conditions, however, are not sufficient to explain the substantial difference between the optical purity of the crude pentachloro-, pentafluoro-, and *p*-nitrophenyl esters. Our results indicate a parallelism between the acidity of the phenol component (p*K* value of PCPOH, 5.3; PFPOH, 5.3; and NPOH, 7.2) and the optical purity of the corresponding ester. Z-Gly-Phe-ODNP (p*K* of DNPOH, 4.1) was obtained in 98% optically pure form,[15] which fact further supports this trend. Even Bz-Leu-OH, which is more sensitive to racemization than the Anderson dipeptide,[14] was converted to a 61% optically pure PCPOH ester by the "reverse" procedure.[16]

(1) This is the seventh in a series of papers concerned with the use of pentachlorophenyl active esters.

(2) (a) J. Kovacs and A. Kapoor, *J. Am. Chem. Soc.*, **87**, 118 (1965); (b) J. Kovacs, R. Ballina, R. L. Rodin, D. Balasubramanian, and J. Applequist, *ibid.*, **87**, 119 (1965); (c) J. Kovacs and B. J. Johnson, *J. Chem. Soc.*, 6777 (1965); (d) J. Kovacs, R. Giannotti, and A. Kapoor, *J. Am. Chem. Soc.*, **88**, 2282 (1966); (e) J. Kovacs, H. N. Kovacs, J. K. Chakrabarti, and A. Kapoor, *Experientia*, **21**, 20 (1965); (f) J. Kovacs and M. Q. Ceprini, *Chem. Ind.* (London), 2100 (1965).

(3) Abbreviations used here are described in "Proceedings of the 5th European Peptide Symposium, Oxford, Sept 1962," G. T. Young, Ed., The Macmillan Co., New York, N. Y., 1963. PCPOH stands for pentachlorophenol, PFPOH for pentafluorophenol, and DNPOH for 2,4-dinitrophenol.

(4) G. W. Anderson and F. M. Callahan, *J. Am. Chem. Soc.*, **80**, 2902 (1958).

(5) M. W. Williams and G. T. Young, *J. Chem. Soc.*, 881 (1963).

(6) M. Goodman and K. C. Stueben, *J. Am. Chem. Soc.*, **81**, 3980 (1959).

(7) To a mixture of N-protected peptide and PCPOH, DCC was added; reactants were present in 1:1:1 molar ratio.

(8) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, 77, 1067 (1955).

(9) "Reverse" DCC procedure means that DCC and 2 to 3 equiv of phenol component were allowed to stand in solution (5–30 min) before addition of the acid.

(10) These "complexes" were prepared by adding 1 mole of DDC to 3 moles of phenol component; the solvent for the DCC–PCPOH "complex" was ethyl acetate, and hexane for the DCC–PFPOH. The "complexes" deposited in crystalline form and were recrystallized from hexane; the melting point for the PCPOH "complex" is 120–165°, and 101.5–102.5° for the corresponding PFPOH "complex," with acceptable analytical values; practically no absorption at 4.7 μ in Nujol or KBr, strong band at 5.95 μ for C=N. Isourea derivatives, similar to "A," of phenols and DCC, are reported in the literature: E. Vowinkel, *Chem. Ber.*, **95**, 2997 (1962); **96**, 1702 (1963); **99**, 42 (1966); F. L. Bach, *J. Org. Chem.*, **30**, 1300 (1965). When the PCPOH "complex" was prepared in DMF, another "complex" was obtained which melted at 104–105.5°. Its analysis indicated a composition between 1 DCC and 2 PCPOH and 1 DCC and 3 PCPOH; based on its infrared spectrum, we believe it contains the above-described "complex" and some N,N′-dicyclohexyl-N-(pentachlorophenyl)urea. However, it is still usable in the preparation of active esters when used in excess; it is designated as "complex" II while the "complex" with the 1:3 ratio is designated as "complex" I. In solution, depending on the solvent, these isourea derivatives dissociate to different extents into the phenol and DCC components, as indicated by the reappearance of the 4.7-μ peak.

(11) In a recent paper D. F. De Tar, *et al.*, *J. Am. Chem. Soc.*, **88**, 1024 (1966), reported that acyl-AA-OH and Z-dipeptides gave extensively (75–100% DL) racemized pentachlorophenyl esters. We believe the differences between their results and ours, concerning the extent of racemization of PCPOH esters, are probably due to different reaction conditions.

(12) (a) The backing-off procedure, which involved the coupling of Z-Gly-OH to HBr·H-Phe-OPCP, gave after recrystallization Z-Gly-Phe-OPCP, mp 160–161°, $[\alpha]^{31}D$ −37.7° (*c* 1.03, chloroform). (b) A recrystallized sample of Z-Gly-Phe-OPFP, prepared by the backing-off procedure, melted at 96–98°, $[\alpha]^{22}D$ −9.8° (*c* 1, chloroform). (c) M. Goodman and K. C. Stueben, *J. Am. Chem. Soc.*, **81**, 3980 (1959), reported mp 146–146.5°, $[\alpha]^{25}D$ −6.5° (*c* 2.0, chloroform) for Z-Gly-Phe-ONP, prepared by the backing-off procedure. We prepared this ester by the usual procedure at −10° (in DMF–EtOAc solution, 20-hr reaction time) in 6% yield and 23% optical purity; the major product isolated was racemic Z-Gly-Phe-OH (60%). Under the same reaction conditions 71.5% Z-Gly-Phe-OPCP was obtained in 90% optical purity. By the "reverse" procedure at 0°, 57% HONP ester of 14% optical purity with correct analysis was obtained as a first crop, and from the mother liquor an additional 18% ester was isolated, which after two recrystallizations gave optically pure ester in 6% yield.

(13) Equimolecular amounts of "complex" I and Z-Gly-Phe-OH reacted in ethyl acetate. Ether was added to the reaction mixture and filtered. The crystalline material, which consisted of DCU and the active ester, was triturated with dioxane and the filtrate evaporated. The crystalline residue was washed with ether. The analyses for the crude materials were correct.

(14) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Am. Chem. Soc.*, **88**, 1338 (1966); *Acta Chim. Acad. Sci. Hung.*, **44**, 51 (1965); M. W. Williams and G. T. Young, *J. Chem. Soc.*, 881 (1963); 3701 (1964).

(15) The usual procedure in the presence of 2 equiv of DNPOH gave, at −10°, 83% crude ester, mp 83–85°, $[\alpha]^{21}D$ −29.1° (*c* 2.01, chloroform). A recrystallized sample melted at 84–85°, $[\alpha]^{21}D$ −30.0° (*c* 2.03, chloroform) and analyzed correctly. In the Anderson test a sample with $[\alpha]D$ −29.8° proved to be optically pure.

(16) Bz-Leu-OPCP, prepared by the backing-off procedure, melted at 125–126°, $[\alpha]^{26}D$ −34.2° (*c* 1.09, chloroform).