Tetrahedron Letters No.20, pp. 1947-1951, 1967. Pergamon Press Ltd. Printed in Great Britain.

THE ^{19}F NMR OF SOME FLUOROQUINOLINES

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(Received 12 August 1966; in revised form 28 January 1967)

In conjunction with other studies of substituted quinolines it was of interest to investigate fluoroquinolines and in particular the ^{19}F NMR spectra of some of these compounds. At the time of completion of this work all the monofluoroquinolines (1) except the 4-fluoro isomer and only one difluoro compound, 2,4-difluoroquinoline (2) were reported. Since then 6,7,8- and 5,6,8-trifluoroquinoline together with the 5,6,7,8-tetrafluoroquinoline (a compound which we also prepared) have been reported (3). Whereas the amount of ^{1}H data on quinolines is slight, there is no previous record of corresponding ^{19}F work. We have obtained the chemical shift data on two new difluoroquinolines, 5,8- and 6,8-difluoroquinoline, together with that for the previously synthesized compounds, 2-fluoro- and 5,6,7,8-tetrafluoroquinoline relative to trifluoroacetic acid, TFAA, as an external standard. The chemical shift data[2] are listed in Table 1 and together with the multiplicities may be observed in the enclosed spectra. Data, but no spectra are included for the new compound, 5-chloro-8-fluoroquinoline.

TABLE 1

Fluoro-quinoline	A	B	C	D
	Chemical Shifts PPM			
2-	-17.51	-	-	-
5,8-	50.12	-	-	-
6,8-	32.80	40.63	-	-
5,6,7,8-	76.03	76.97	80.96	83.76
5-Cl-8-	44.36	-	-	-

The spectrum of 2-fluoroquinoline (Fig. 1 and 2) at room temperature gave a single broad

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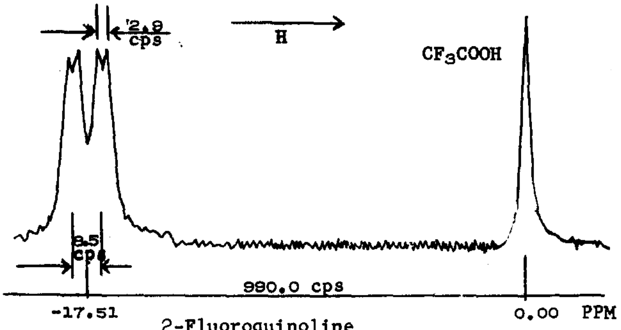
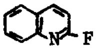
[2] The ^{19}F NMR spectra were obtained on a Varian DP 60 instrument operating at 56.441 MHz. The spectra were calibrated by generating 2054 Hz sidebands, therefore the chemical shifts are reported to four figures. The ^{1}H work was obtained on a Varian A 60 using a TMS-$CHCl_3$ solution previously calibrated on the DP 60. The spectra are presented with the field strength increasing from left to right.

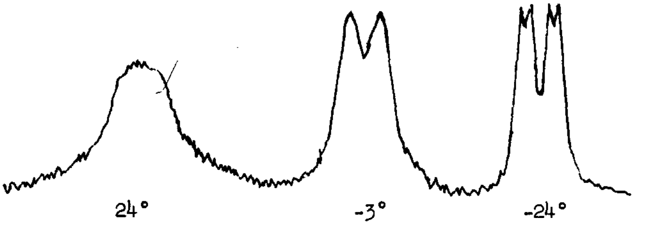
FIGURE 1



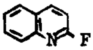


2-Fluoroquinoline
CCl_4 100 mg./ml.

FIGURE 2

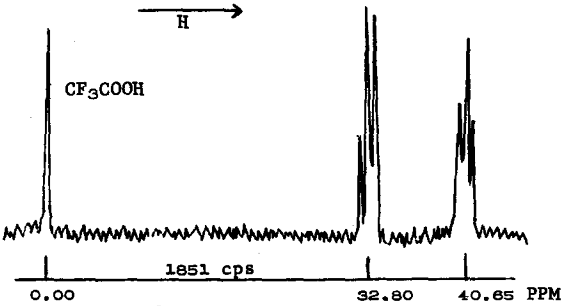


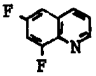
Temperature Dependence of Resolution



2-Fluoroquinoline

FIGURE 3





6,8-Difluoroquinoline
CCl_4 100 mg./ml.

peak downfield from trifluoroacetic acid. A similar line broadening effect was found for the 2-position fluorine in polyfluoropyridines (4). However, it was found that by cooling the sample the broad peak could be resolved into the expected quartet giving $J_{2_F-3_H}$ of 8.5 cps and $J_{2_F-4_H}$ of 2.9 cps. We interpret this line broadening as small ^{14}N spin-spin splitting which is removed by more effective quadrupole relaxation of the ^{14}N spin states at lower temperatures. This interpretation has also been proposed to explain temperature effects of NF_3 fluorine NMR but over a range of 225° (5). No 2-position proton line broadening is found in quinoline.

The spectrum of 6,8-difluoroquinoline (Fig. 3) (m.p. 65-67°) gives two resonance peaks, a low field quartet (24.8 cps width) which we attribute to the 6-position fluorine and a triplet (19.2 cps width) at higher field assigned to the 8-position fluorine. The symmetry of the absorption peaks requires that the three ortho-J_{HF} ($J_{5_H-6_F}$, and $J_{7_H-6_F}$, and $J_{7_H-8_F}$) and the meta-J_{FF} be of equal magnitude. The fact that the 8-fluorine peak is a triplet also requires a para-$J_{5_H-8_F}$ of zero magnitude. A para J_{HF} of zero has been found for fluorobenzene (6). However, the coupling constants determined from the multiplet widths are unequal. We thus feel that 6,8-difluoroquinoline is an example of what has become known as "virtual" coupling.

The new compound, 5,8-difluoroquinoline, (Fig. 4) (m.p. 70-71°) gives a very surprising ^{19}F NMR spectrum. Where two resonance absorption multiplets would be expected and in spite of the "lean" towards higher field by the outer numbers of a triplet at 50.12 PPM (13.9 cps width), no second resonance peak was found. A search was made for a possible second peak for over an additional 19 MHz upfield and downfield. In order to confirm this as the true ^{19}F spectrum it was repeated at 19.3 MHz which still gave the same single triplet with the same width of 13.9 cps. A further additional check was obtained by the integration of an equimolar mixture of 5,8- and 6,8-difluoroquinoline, the three multiplets of which gave a 1:1:2 ratio with increasing field strength.[3] An interesting side effect of this equimolar mixture was that the upfield triplet increased in complexity. That this partial removal of fluorine equivalence was due to a "specific complex" formation was shown by dilution with solvent. No changes in the downfield multiplets of the 6,8-difluorocompound were observed while the 50 PPM region of the 5,8-isomer went from a triplet in its pure solution to a four and finally seven peak

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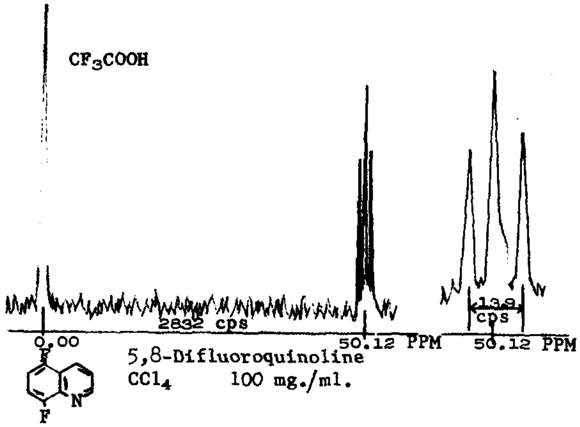
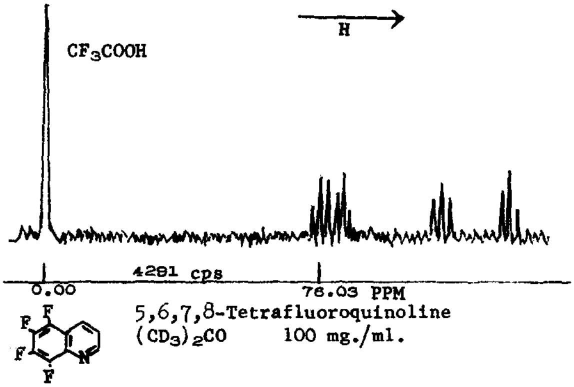
[3] Suggested by the referee.

FIGURE 4



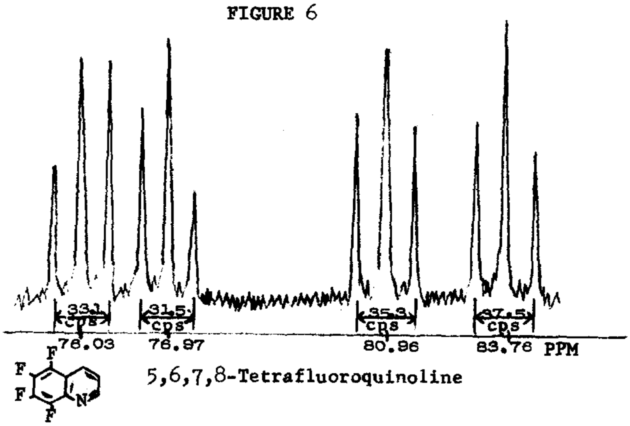
5,8-Difluoroquinoline
CCl_4 100 mg./ml.

FIGURE 5



5,6,7,8-Tetrafluoroquinoline
$(CD_3)_2CO$ 100 mg./ml.

FIGURE 6



5,6,7,8-Tetrafluoroquinoline

multiplet in the mixture under extreme dilution. The spectrum of 5,8-difluoroquinoline is thus another example of "virtual" coupling and must await future double resonance and solvent dependence experiments. Although deuterium substitution and double irradiation were used to remove the "virtual" coupling found in fluorobenzene (6) thus far we have been unable to effect deuterium exchange using D_2O under a variety of conditions in any of our quinoline compounds.

The ^{19}F spectrum of 5,6,7,8-tetrafluoroquinoline (Fig. 5 and 6) in D_6-acetone shows four sets of triplets. In contrast to the case of 5,8-difluoroquinoline, considerable internal chemical shift is found. Again we may be seeing "virtual" coupling but an alternate possibility exists. The meta-J_{FF} in fluoroaromatics is of smaller magnitude (and in some cases equal to zero) than either ortho-J_{FF} or para-J_{FF} (7). Determination of the relative order of chemical shifts and verification of the proposed zero absolute magnitude of all meta-J_{FF}'s in this compound must await future double resonance experiments.

The only cross-ring spin-spin coupling found in the parent compound, quinoline, has been shown to be a J_{4H-8H} of 0.8 cps (8). The 4-proton pattern in the ^1H spectrum of 5,8-difluoroquinoline shows a resonance absorption unlike that in the parent compound. With analysis of this apparent cross-ring coupling in mind, 5-chloro-8-fluoroquinoline (m.p. 61-62°) was synthesized. The ^1H pattern of the 4-proton (a pair of triplets) has proven to be identical to that found in 5,8-difluoroquinoline. We determine this cross-ring J_{4H-8F} coupling to be 1.5 ± 0.1 cps or approximately double that found in the corresponding proton coupling of quinoline. The ^{19}F NMR shows the expected quartet of doublets (at 44.36 PPM) again giving the J_{4H-8F} of 1.5 cps together with J_{6H-8F} of 4.2 cps and J_{7H-8F} of 8.7 cps.

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