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REACTION OF o-ARYLENEDIAMINES WITH ETHYL 3-FLUORO 2-KETOESTERS SYNTHESIS OF QUINOXALINE DERIVATIVES

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SUMMARY

The reaction of o-arylenediamines with ethyl 3-fluoro-2-keto esters was studied. Fluoroquinoxaline derivatives characterized by their spectroscopic properties, were obtained in good yields. I.R. spectra, in particular, presented a very strong band at 1660-1667 cm^{-1} characteristic of $\nu_{C=O}$ amide, indicating that the condensation products exist predominately in the keto form.

INTRODUCTION

An earlier study in our laboratory involved a general synthesis of fluoropyruvic acid derivatives [1] . The reactions of these fluorinated compounds towards amines were examined and led to Schiff's bases and hydrazones [2] . The conversion of these last products into the corresponding fluorinated aminoacids was examined but this approach still has not been successful. We continue to explore the reduction of Schiff's bases, oximes and hydrazones to the desired fluoro aminoacids.

However, the reactions of ethyl 3-fluoro 2-keto 3-methyl butanoate and ethyl 3-fluoro 2-keto 3-methyl pentanoate with o-phenylenediamine give good yields of 3-fluoroalkyl 2-oxo 1,2-dihydroquinoxalines [2] .

Quinoxaline derivatives have been proven to be important classes of compounds possessing pharmacological properties [3,4,

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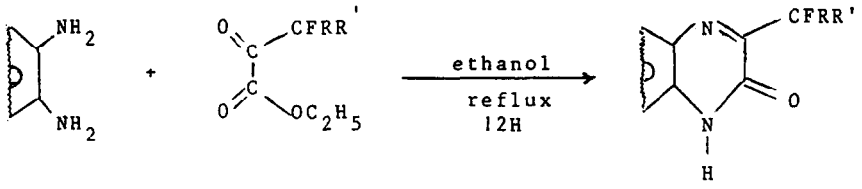
5,6,7a,7b,] . It seemed worthwhile to study the reactions of 3-fluoro 2-keto esters with different o-arylenediamines. The results of that study are now being reported.

RESULTS

The formation of these new products can be understood from the following reaction scheme :



The results are summarized in Table I recording Experimental details and yields of recrystallized pure products. Products 3-17 are new compounds.

TABLE 1

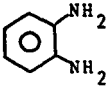
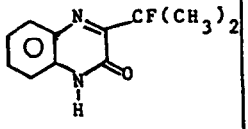
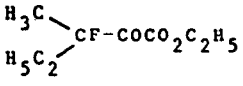
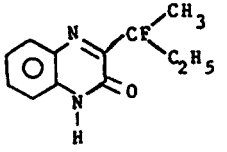
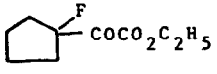
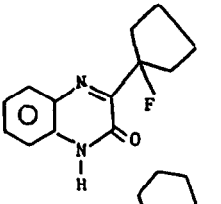
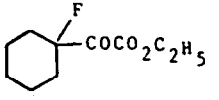
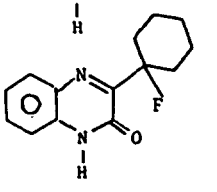
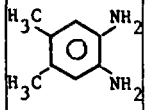
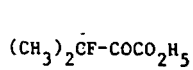
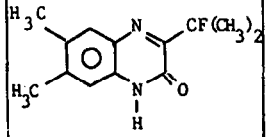
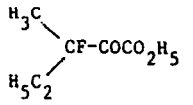
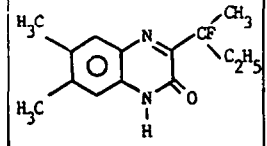
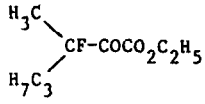
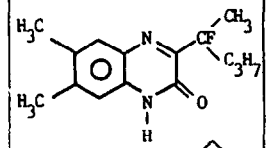
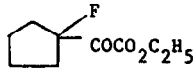
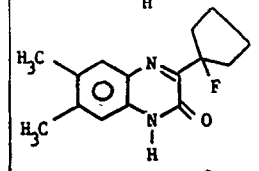
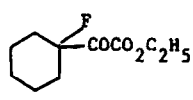
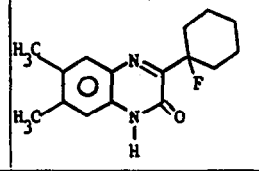
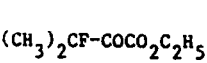
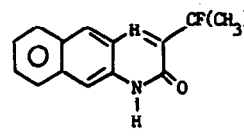
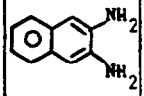
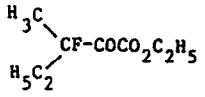
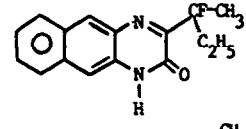
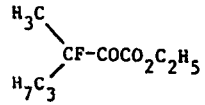
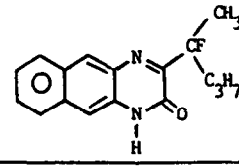
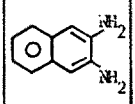
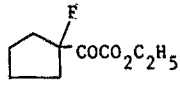
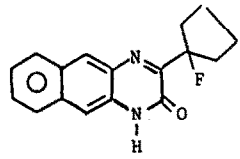
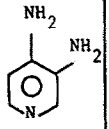
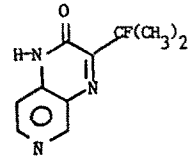
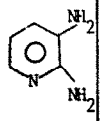
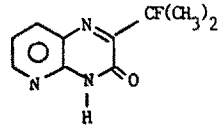
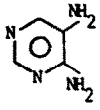
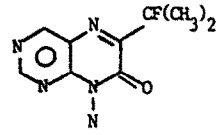
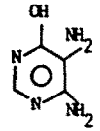
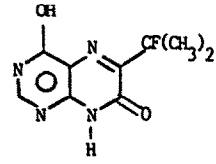
Amine	Ketoester	Products	N°	Yield %	m.p.[a] °C
	$(CH_3)_2CF-COCO_2C_2H_5$		1	70	150-152
			2	60	157-158
			3	63	169-171
			4	70	205-206

TABLE 1 (cont.)

Amine	Ketoester	Products	N°	Yield %	m.p.[a] °C
			5	70	178-179
			6	65	189-191
			7	65	160-163
			8	60	175-177
			9	60	181-182
			10	65	195-198
			11	60	179-181
			12	60	175-177

(Continued overleaf)

TABLE 1 (cont.)

Amine	Ketoester	Products	N°	Yield %	m.p.[a] °C
			13	65	189-190
	$(CH_3)_2CF\text{-}COCO_2C_2H_5$		14	65	220-223
	$(CH_3)_2CF\text{-}COCO_2C_2H_5$		15	60	210-212
	$(CH_3)_2CF\text{-}COCO_2C_2H_5$		16	57	181-183
	$(CH_3)_2CF\text{-}COCO_2C_2H_5$		17	55	197-200

[a] Melting points are uncorrected.

The products were characterized by their spectroscopic properties. I.R., NMR (^{1}H and ^{19}F) and mass spectra analysis are summarized in Table 2.

TABLE 2
spectra data

Compound	IR (cm^{-1}) $\nu C{=}O$	IR (cm^{-1}) $\nu C{=}C$	^1H NMR δ, ppm	^{19}F NMR ϕ, ppm	Mass spectrum
1	1667	1615	1.8(d,6H,$(CH_3)_2CF$, $^3J_{FH}$=22Hz); 7.3-7-6 (m,4H,C_6H_4)	149,2 (septet)	m/e 206 (M^+ 27%); 187 (M- F 15%); 186 (M-HF 100%)
2	1667	1614	1(t,3H,CH_3CH_2); 1.9 (d,3H,CH_3CF, $^3J_{FH}$=22Hz) 7.4-7.7(m,4H,C_6H_4)	159,4 (sextuplet)	m/e 220 (M^+ 11%); 146 (Mc Lafferty rearrangement 21% ; 90(100% $C_6H_4N^+$)
3	1665	1610	1.9-2.5(m,8H,$(CH_2)_4$) 7.4-7.9(m,4H,C_6H_4)	143.9 (m)	m/e 232(M^+ 15%); 213 (M-F 16.5%);212 (M-HF 100%)
4	1666	1611	1.7-2.5(m,10H,$(CH_2)_5$) 7.2-7.8(m,4H,C_6H_4)	161.2 (m)	m/e 246(M^+ 22%); 227 (M-F 18%);226(M-HF, 100%)
5	1660	1610	1.9(d,6H,$(CH_3)_2CF$, $^3J_{FH}$=22Hz);2.35(s, 6H,$(CH_3)_2$-C_6H_2); 7.1-7.6(m,C_6H_2)	141.9 (m)	m/e (M^+ 234 37.2%) 215 (M-F 13%) ; 214 (M-HF 54.7%)
6	1660	1610	1(t,3H,CH_2CH_3); 1.9 (d,3H,CH_3CF, $^3J_{FH}$= 22Hz); 2.3(s,6H, $(CH_3)_2$-C_6H_2); 7.1-7.6 (m,C_6H_2)	152.3 (sextuplet)	m/e 248 (M^+ 10.4%); 229 (M-F 14.8%); 228 (M-HF 74.2%) ; 174 (Mc Lafferty rearrangement 15%)
7	1660	1610	1-1.5(m,7H,C_3H_7); 1.9(d,3H,CH_3CF, $^3J_{FH}$=22Hz);2.3(s, 6H, $(CH_3)_2$-C_6H_2); 7.2-7.8 (m,C_6H_2)	149.9 (sextuplet)	m/e 262 (M^+ 9.6%); 243 (M-F 9.5%): 242 (-HF, 42.8%); 227 ($C_{13}H_{13}N_2O^+$ 100%)
8	1662	1611	1.8-2.7(m,8H,$(CH_2)_4$) 2.4(s,6H,$(CH_3)_2$-C_6H_2) 7.1-7.7 (m,C_6H_2)	143.4 (m)	m/e 260 (M^+ 24.7%); 241 (M-F 21%); 240 (M-HF 100%)
9	1662	1611	1.7-2.5(m,10H,$(CH_2)_5$); 2.4(s,6H,$(CH_3)_2$-C_6H_2); 7.1-7.6 (m,C_6H_2)	160.9 (m)	m/e 274 (M^+ 24%); 255 (M-F 12%); 254 (M-HF 55%)

(Continued overleaf)

TABLE 2 (cont.)
spectra data

Compound	IR (cm^{-1}) UC=O	UC=C	^{1}H NMR δ, ppm	^{19}F NMR Ø, ppm	Mass spectrum
10	1665	1635	1.9(d,6H,$(CH_3)_2CF$ $^3J_{FH}$=22Hz);7.1-8.3 (m,6H,$C_{12}H_6$)	140.7 (septet)	m/e 256 (M^+ 28.7%); 237(M-F 5%); 236(M-HF 25.7%)
11	1665	1635	1(t,3H,CH_2CH_3); 1.9 (d,3H,CH_3CF, $^3J_{FH}$= 22Hz); 7-8.3 (m,6H, $C_{12}H_6$)	152 (septuplet)	m/e 270 (M^+ 15%); 251(M-F 18%); 250(M-HF 40%)
12	1665	1635	0.9-1.5(m,7H,C_3H_7) 1.9(d,3H,CH_3CF, $^3J_{FH}$=22Hz);7-8.3 (m,6H,$C_{12}H_6$)	149.7 (sextuplet)	m/e 284 (M^+ 49%); 265 M-F 83%) 264 (M-HF 78.4)
13	1665	1634	1.8-2.7(m,8H$(CH_2)_4$) 7-8.3(m,6H,$C_{12}H_6$)	144 (m)	m/e 282 (M^+ 2.8%); 263 (M-F 3.9%) 262 (M-HF 15%)
14	1667	1610	1.9(d,6H,$(CH_3)_2CF$ $^3J_{FH}$=22Hz);7.1-8.4 (m,3H,C_5NH_3)	141.6 (septet)	m/e 207 (M^+ 25%) 188 (M-F 14.5%) 187 (M-HF 100%)
15	1667	1610	1.86(d,6H,$(CH)_2CF$, $^3J_{FH}$=22Hz);7.3-8.5 (m,3H,C_5NH_3)	143.5 (septet)	m/e 207 (M^+ 76%); 188 (M-F 30%) 187 (M-HF 100%)
16	1668		1.5(d,6H,$(CH_3)_2CF$ $^3J_{FH}$=22Hz);7.8-8.3 (m,2H,$C_4N_2H_2$)	142 (septet)	m/e 208 (M^+ 68.3%); (chemical ionization)
17	1667		1.7(d,6H,$(CH_3)_2CF$, $^3J_{FH}$=22Hz);7.4(s, 1H,C_4N_2OH)	142.3 (septet)	m/e 224 (M^+ 10%); 205 (M-F 5%) ; 204 (M-HF 18%)

- I.R. spectra were measured in KBr disks.
- All of the ^{1}H and ^{19}F NMR spectra were taken in solutions in $(CD_3)_2SO$.
- Chemical shifts for ^{1}H and ^{19}F NMR spectra are given in δppm Upfield from ext. TMS and in δppm from ext. CCl_3F respectively.

DISCUSSION

The reactions are analogous to those of keto acids or esters in the hydrocarbon series [8,9]. Some perfluoro-substituted quinoxaline derivatives obtained from either perfluoroalkyl α,β -diketones or perfluoroalkylketoesters have been reported [10].

Reactions with the corresponding 3-fluoro 2-oxo acid derivatives led to Schiff's bases. However, when ethyl 3-fluoro 2-ketoesters were used fluoroalkyl oxo dihydroquinoxalines (1-17) were obtained in one step, in reasonable yields.

The products were characterized, by their spectroscopic properties, confirming the structure of the products as we observed earlier from ethyl 2-keto 3-fluoro 3-methyl butanoate and ethyl 2-keto 3-fluoro 3-methyl pentanoate [2].

In every case, the I.R. spectra indicate the presence of a strong band at 1660-1667 cm^{-1} corresponding to the ν C=O amide. In contrast, we detected only weak absorption at 3300- 3400 cm^{-1} characteristic of OH, showing that the products (1-17) exist mainly as keto-forms. The results match the conclusion of a recent study of Bertrand et al. who determined the structure of 3-methyl 2-oxo-benzo(g)quinoxaline by X-ray diffraction [11] .

EXPERIMENTAL

All melting points are uncorrected. The I.R. spectra were recorded on a Leitz Model III G. ^{1}H NMR spectra were measured on a Varian EM 360 (60 MHz) and on a Bruker spectrospin W 80 (80 MHz) instruments.

^{19}F NMR spectra were recorded on a Bruker spectrospin WH 30 DS (84.67 MHz). Mass spectra were determined on a Ribermag 10-10 instrument.

General procedures

An ethanol solution of ethyl 3-fluoro 2-ketoester and o-arylenediamine was heated under reflux for 12 hours. After evaporation of the solvent, the solid residue was crystallized from a benzene/ethanol mixture.

Reaction of o-phenylenediamine with ethyl 2-keto 3-fluoro 3-methyl butanoate (compound 1)

$(CH_3)_2CFCOCO_2C_2H_5$ (1 g, 6.17 mmol) was added to an ethanol (10-20 ml) solution of o-phenylenediamine (0.66 g, 6.17 mmol). The solution was refluxed for 12 H. After evaporation of the solvent, the solid residue was recrystallized from benzene/ethanol (9/1 v/v). Compounds 2-4 were made similarly.

Synthesis of compound 5 from 4,5-dimethyl o-phenylenediamine.

This product was obtained in the same manner as compound 1.

Synthesis of compound 10 from 2,3-diaminonaphthalene

$(CH_3)_2CFCOCO_2C_2H_5$ (0.4 g, 2.46 mmol) was added to hot ethanol (15 ml) containing 2,3-diaminonaphthalene (0.3 g, 2.46 mmol). The mixture was refluxed for 12 h. After evaporation of the solvent and recrystallization from benzene/ethanol, a yellow crystalline product was obtained.

- Compounds 14-17 were obtained from the corresponding diamine and $(CH_3)_2CFCOCO_2C_2H_5$ in the same manner as described above.

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