*Heterocyclic Fluorine Compounds. Part II.** Bz-*Monofluoroindoles.*

By F. L. Allen, J. C. Brunton, and H. Suschitzky.

[Reprint Order No. 5904.]

The four *Bz*-monofluoroindoles have been made by a Fischer synthesis. 4- and 6-Fluoroindole were also prepared by an unequivocal method.

4-, 5-, 6-, and 7-FLUOROINDOLE have been prepared by a Fischer cyclisation of ethyl pyruvate *o*-, *m*-, and *p*-fluorophenylhydrazone, respectively, followed by hydrolysis and decarboxylation. The required hydrazones were obtained from the fluorophenylhydrazines (Suschitzky, *J.*, **1953**, **3326**), and also by a Japp–Klingemann reaction with the corresponding diazotised fluoroanilines. Ring closure of the *m*-fluorophenylhydrazone led to a mixture of ethyl 4- and 6-fluoroindole-2-carboxylate, the latter in large excess perhaps owing to the strong *para*-directing influence of fluorine; only the 6-fluoro-isomer could be isolated, the presence of the 4-fluoro-compound being inferred from the ultra-violet absorption.

Since authentic specimens of these two compounds were needed as reference compounds in the ambiguous cyclisation of ethyl pyruvate *m*-fluorophenylhydrazone, they were also made by an alternative route. Ethyl 6-fluoroindole-2-carboyxlate was obtained by a Reissert synthesis: condensation of 4-fluoro-2-nitrotoluene (*idem, loc. cit.*) with diethyl oxalate in the presence of potassium ethoxide afforded the potassium derivative of the keto-ester which, on alkaline reduction, yielded a mixture of the 6-fluoroindole acid and its ethyl ester. Ethyl 4-fluoroindole-2-carboxylate was made by a similar sequence of reactions. We failed to separate 2-fluoro-6-nitrotoluene, the starting material, from the nitration product of *o*-fluorotoluene by fractional distillation, as described by Schiemann (*Ber.*, 1929, **62**, 1794). It was readily obtained, however, by refluxing the nitration

---

* Part I, *J.*, **1953**, **3845**.

product in alcoholic potassium hydroxide (which converted the unwanted 2-fluoro-5-nitrotoluene into an ethyl ether), followed by fractionation. Cyclisation produced here only 4-fluoroindole-2-carboxylic acid. Treatment of its silver salt with ethyl iodide furnished the ester and an acidic by-product which agreed analytically with an ethyl-substituted monofluoroindolecarboxylic acid. We regard this compound as 3-ethyl-4-fluoroindole-2-carboxylic acid, because it possesses no ethylimino-group, and its nitroso-derivative gives a positive Liebermann's test (Verkade, Lieste, and Werner, *Rec. Trav. chim.*, 1945, **64**, 289).

Hydrolysis of the above esters followed by heating the resulting acids above their melting points yielded the four *Bz*-fluoroindoles. The use of lime for the decarboxylation (Ciamician and Zatti, *Ber.*, 1889, **22**, 197) gave poor yields.

Ultra-violet absorption maxima (*m*μ) *in ethanol.*

							Ethyl indole-2-carboxylate			
Indoles	λ_1	ε_1	λ_2	ε_2	λ_3	ε_3	λ_1	ε_1	λ_2	ε_2
4-F	216	42,000	265	5600	284·5	2000	232	29,000	287	17,000
5-F	218	22,000	280	6600	295·5	4100	218	20,000	291	19,500
6-F	216	33,000	275	5100	—	—	217	22,000	299	18,000
7-F	214	30,000	262	4300	285	2000	240	12,000		
							232	27,000	286	17,500

Data for the absorption spectra of both the fluorine-substituted indoles and monofluoro-carbethoxy-indoles are given in the accompanying Table.

EXPERIMENTAL

Light petroleum had b. p. 60—80° and ligroin b. p. 80—100°. Ultra-violet spectra were determined in ethanol with a Unicam spectrophotometer S.P. 500.

Preparation of Ethyl Pyruvate Fluorophenylhydrazones.—(*a*) Equimolar quantities of ethyl pyruvate and the requisite fluorophenylhydrazine were heated together on a water-bath for 0·5 hr. The solid obtained on cooling was collected and crystallised from aqueous ethanol.

(*b*) A solution of diazotised *o*-, *m*- or *p*-fluoroaniline in concentrated hydrochloric acid (19 c.c.) and water (15 c.c.) was added to ethyl α-methylacetoacetate (7·2 g.) dissolved in 50% aqueous potassium hydroxide (17 c.c.) and ethanol (65 c.c.). Dilution of the red reaction mixture with water yielded a precipitate which was recrystallised from ethanol. The *ortho*-isomer separated first as a syrup, but crystallised in contact with ether. Mixed m. p.s of specimens from the two methods were undepressed.

Ethyl pyruvate o-*fluorophenylhydrazone* (38%), m. p. 113—114°, was obtained as pale yellow needles from chloroform–ligroin (1 : 1) (Found : N, 12·8. $C_{11}H_{13}O_2N_2F$ requires N, 12·5%); the meta-*isomer* (55%), colourless plates from ethanol, had m. p. 103° (Found : N, 12·2%), and the para-*isomer* [(*a*) 37%; (*b*) 55%], m. p. 90—91°, crystallised in colourless needles from aqueous ethanol (Found : N, 12·2%).

Cyclisation of Ethyl Pyruvate Fluorophenylhydrazones.—Each of the ethyl pyruvate fluorophenylhydrazones (4·5 g.) was cyclised in a boiling mixture of acetic acid (30 c.c.) and concentrated sulphuric acid (1·5 c.c.) during 5—15 min. Addition of water precipitated a crude product which was taken up in ether. After being washed free from acid (10% aqueous sodium carbonate) and dried ($MgSO_4$), the ethereal extract was evaporated to a nearly colourless solid. Ethyl pyruvate *m*-fluorophenylhydrazone gave a mixture of isomers which was first chromatographed (aluminium oxide; benzene–light petroleum, 10 : 1) and then fractionally crystallised (from light petroleum–benzene, 1 : 1). Ethyl 4-fluoroindole-2-carboxylate was obtained in an impure state from the isomeric mixture as the more strongly adsorbed and more soluble constituent, m. p. 108—112°, raised to 118° on admixture with an authentic specimen. Light absorption max. of the impure sample λ_1 233, λ_2 288 mμ (ε, 26,000; ε_2 16,500); this corresponds to *ca.* 75% of pure compound.

In another experiment a suspension of the silver salt (1·5 g.) of 4-fluoroindole-2-carboxylic acid (see below) in benzene was heated with ethyl iodide (1·0 g.) under reflux for 24 hr. The solid was filtered off, and the benzene solution, after extraction with sodium carbonate solution (10%) and drying ($MgSO_4$), yielded on evaporation *ethyl* 4-*fluoroindole*-2-*carboxylate* (38%) as white needles (from aqueous ethanol), m. p. 121° (Found : N, 6·5. $C_{11}H_{10}O_2NF$ requires

N, 6·8%). Acidification of the sodium carbonate extract gave a white solid (0·4 g.) of m. p. 205°, recrystallisable as needles from ethanol (Found: C, 63·7; H, 5·0; N, 7·0; NEt, 0%; equiv., 204·1. $C_{11}H_{10}O_2NF$ requires C, 63·8; H, 4·8; N, 6·8%; equiv., 207). Its nitroso-compound, prepared in glacial acetic acid by addition of sodium nitrite, gave a positive Liebermann reaction, and this substance is, therefore, regarded as 3-*ethyl*-4-*fluoroindole*-2-*carboxylic acid.* Light absorption max.: 231 (ε 33,000) and 288 mμ (ε 13,000).

Ethyl 5-*fluoroindole*-2-*carboxylate* (65%) crystallised as needles (from ethanol), m. p. 148° (Found: N, 6·9%).

Ethyl 6-*fluoroindole*-2-*carboxylate.* (*a*) This *ester* was obtained pure from the mixture of isomers (see above) as the less adsorbed and less soluble constituent. When recrystallised from chloroform–light petroleum it had m. p. 143° (Found: N, 6·9%).

(*b*) 4-Fluoro-2-nitrotoluene (30 g.) (Suschitzky, *loc. cit.*; Steck and Fletcher, *J. Amer. Chem. Soc.*, 1948, **70**, 439) reacted with ethyl oxalate (24·6 g.) in ether (250 c.c.) in the presence of potassium ethoxide (from 7·8 g. of potassium and 55 c.c. of ethanol) at room temperature. After 48 hr. the red potassium salt (60%) was collected and dried. Acidification (dilute sulphuric acid and ether) of a portion of the salt gave *ethyl* 4-*fluoro*-2-*nitrophenylpyruvate*, m. p. 54°, as yellow needles (Found: N, 5·5. $C_{11}H_{10}O_2NF$ requires, N, 5·5%). The bulk of the potassium salt (29·3 g.), suspended in 460 c.c. of dilute aqueous ammonia (from 210 c.c. of solution of *d* 0·880), was reduced by adding a hot solution of ferrous sulphate (220 g.) in water (250 c.c.). The reaction mixture was boiled for 3 hr. and then filtered. Addition of acid to the filtrate deposited 6-fluoroindole-2-carboxylic acid (see below). The ethereal extracts of the iron residues gave ethyl 6-fluoroindole-2-carboxylate on evaporation as white leaflets (22%), m. p. 142—143°, unchanged on admixture with a sample obtained as in (*a*).

Ethyl 7-*fluoroindole*-2-*carboxylate* (50%) was obtained as white needles (from ethanol), m. p. 140° (Found: N, 7·0%).

Preparation of the Fluoroindoles-2-*carboxylic Acids.*—The ethyl esters above described were hydrolysed with aqueous-ethanolic sodium hydroxide. The acids were conveniently purified as their ammonium salts.

4-*Fluoroindole*-2-*carboxylic Acid.*—The isomeric mixture of nitro-compounds (89%) obtained by nitration of *o*-fluorotoluene (200 g.) (Schiemann, *loc. cit.*) was boiled under reflux for 1 hr. with aqueous-ethanolic 0·5N-potassium hydroxide (500 c.c.; 60% ethanol). Addition of brine precipitated an oil which was run off, washed with brine, and dried ($MgSO_4$). Fractionation gave 2-fluoro-6-nitrotoluene (10%; calc. on *o*-fluorotoluene), b. p. 91—92°/8 mm. (*idem, loc. cit.*, gives b. p. 97—97·2°/11 mm.). The residual liquid solidified and yielded nearly colourless needles of 2-ethoxy-5-nitrotoluene, m. p. 71° (from ethanol) (Found: N, 7·8. Calc. for $C_9H_{11}O_3N$: N, 7·7%). Staedel (*Annalen*, 1883, **217**, 153) records m. p. 71°. 2-Fluoro-6-nitrotoluene (15 g.) was caused to react with ethyl oxalate (17·3 g.) in the presence of potassium ethoxide as described for the preparation of ethyl 6-fluoroindole-2-carboxylate. Reductive ring-closure of the salt (19 g.) as before gave 4-*fluoroindole*-2-*carboxylic acid* (2·3 g., 20%) as white needles (from aqueous ethanol), m. p. 219—220° (decomp.) (Found: N, 7·9%; equiv., 183. $C_9H_6O_2NF$ requires N, 7·8%; equiv., 179). Another 2 g. of this acid (17%) was obtained by extraction of the iron residues with ether followed by hydrolysis of the oily extract.

5-*Fluoroindole*-2-*carboxylic acid* (81%) recrystallised from aqueous ethanol as white needles, m. p. 248—249° (decomp.) (Found: N, 8·0%; equiv., 182).

6-*Fluoroindole*-2-*carboxylic Acid.*—(*a*) This acid formed leaflets (91%) (from aqueous ethanol), m. p. 246° (decomp.) (Found: N, 7·8%; equiv., 184).

(*b*) The acid (36%), prepared by a Reissert synthesis from 4-fluoro-2-nitrotoluene (see above), crystallised as white leaflets and had m. p. 245—246°, alone and mixed with the previous sample.

7-*Fluoroindole*-2-*carboxylic acid* (75%) was obtained as white leaflets, m. p. 198° (decomp.) (Found: N, 7·5%; equiv., 182).

Fluoroindoles.—The fluoroindolecarboxylic acids were heated above their m. p. until sublimation ceased (5—10 min.). Steam-distillation and recrystallisation furnished the colourless indoles.

4-*Fluoroindole* (80%) crystallised as white needles (from ligroin), m. p. 30° (Found: C, 71·6; H, 4·6; N, 10·5. C_8H_6NF requires C, 71·4; H, 4·5; N, 10·4%). It gave a *picrate* of orange-red needles (from benzene), m. p. 164—166° (Found: N, 15·3. $C_{14}H_9O_7N_4F$ requires N, 15·4%), and a *s*-*trinitrobenzene* derivative of orange-yellow needles (from ethanol), m. p. 172° (Found: N, 15·7. $C_{14}H_9O_6N_4F$ requires N, 15·5%).

5-*Fluoroindole* (52%), white leaflets (from ligroin), m. p. 46° (Found: C, 71·0; H, 4·5; N, 10·0%), gave a *picrate*, orange needles (from benzene), m. p. 155—156° (Found: N, 15·8%), and a s-*trinitrobenzene* derivative, yellow needles (from ethanol), m. p. 160° (Found : N, 15·7%). The use of lime for the decarboxylation of this acid (Ciamician and Zatti, *loc. cit.*) gave a low yield (22%).

6-*Fluoroindole*. (*a*) The *compound* formed white needles (51%), m. p. 75°, from aqueous ethanol (Found : C, 71·0; H, 4·9; N, 10·0%), and gave a *picrate*, orange-red needles (from benzene), m. p. 147—148° (Found : N, 15·1%), and a s-*trinitrobenzene* derivative, orange-yellow needles (from ethanol), m. p. 151° (Found : N, 15·8%).

(*b*) 6-Fluoroindole-2-carboxylic acid (0·9 g.) and freshly prepared cuprous chloride (0·5 g.) were suspended in quinoline (25 c.c.) and refluxed for 3 hr. (Uhle, *J. Amer. Chem. Soc.*, 1949, **71**, 761). The mixture was poured on ice (150 g.) and concentrated hydrochloric acid (25 c.c.) and then extracted with ether. Evaporation of the ethereal layer furnished the acid as white needles (0·3 g., 44%), m. p. 74—75°.

7-*Fluoroindole* (48%) was obtained as white unstable crystals (from aqueous ethanol), m. p. 61—62° (Found : N, 10·7%). The *picrate* crystallised as orange-red needles, m. p. 154—155°, from benzene (Found : N, 15·7%).

We thank the Department of Scientific and Industrial Research for the award of a maintenance grant to one of us (J. C. B.).

WEST HAM COLLEGE OF TECHNOLOGY, WEST HAM, E.15. [*Received, November 23rd*, 1954.]