139. *Heterocyclic Fluorine Compounds. Part IV.* Monofluoroindazoles.*

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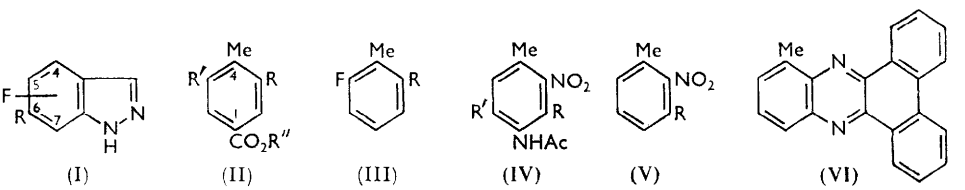
5-, 6-, and 7-Fluoroindazole (I; R = H) have been prepared by a Balz–Schiemann reaction of the corresponding aminoindazoles. Their ethyl 6-carboxylates (I; R = CO_2Et) have also been obtained by cyclising the requisite *N*-nitroso-*N*-*o*-tolylbenzamide in dry benzene. Attempts to prepare the 4-fluoro-isomer by a route different from that described elsewhere failed.

All the *Bz*-mononitroindazoles required in our work were made by diazotisation of the respective nitro-*o*-toluidines in acetic acid.[1] 3-Nitro-*o*-toluidine (NH_2 = 1), the starting material for 4-nitroindazole, was prepared by reduction of 2,4,6-trinitrotoluene at position 4, followed by deamination with hypophosphorous acid and mono-reduction of the resulting 2,6-dinitrotoluene with ammonium sulphide.

Reduction of nitroindazoles with iron and water containing a little hydrochloric acid [2] generally gave aminoindazoles in good yield, although it led to some decomposition in the case of the 4- and the 7-amino-compound (cf. Davies [3]). While 5-, 6-, and 7-fluoroindazole were readily obtained from these amines by a Balz–Schiemann reaction, 4-aminoindazole behaved abnormally on diazotisation, possibly because of its structural resemblance to *m*-phenylenediamine.



(I) (II) (III) (IV) (V) (VI)

From crude indazole-7-diazonium borofluoride, which had to be prepared in hydroborofluoric acid at −10°, a small quantity of a brown, water-insoluble solid was separated. It was thought to be a triazole in view of the formal resemblance between 7-aminoindazole and *o*-phenylenediamine. Attempts to purify it, however, failed.

4-Fluoroindazole was synthesised as follows: 3,5-dinitro-*p*-toluic acid (II; R = R′ = NO_2, R″ = H) was reduced to a mixture of 3-amino-5-nitro-*p*-toluic acid and the diamine which were separable by fractional crystallisation of their ethyl esters. A Balz–Schiemann reaction on the nitro-ester (II; R′ = NH_2, R = NO_2, R″ = Et) followed by hydrolysis and decarboxylation gave 2-fluoro-6-nitrotoluene (III; R = NO_2). From it *N*-(3-fluoro-*o*-tolyl)benzamide was obtained (identical with a sample prepared by another method [4])

* Part III, *Tetrahedron*, 1959, **6**, 315.

[1] Porter and Petersen, *Org. Synth.*, Coll. Vol. III, p. 660.
[2] Petitcolas and Sureau, *Bull. Soc. chim. France*, 1950, 3959.
[3] Davies, *J.*, 1955, 2412.
[4] Suschitzky, *J.*, 1955, 4026.

which was cyclised *via* its nitroso-compound in benzene to 4-fluoroindazole. Decarboxylation, by the usual methods, of 4-fluoroindazole-6-carboxylic acid (I; R = CO_2H) obtained from ethyl 3-fluoro-5-nitro-*p*-toluate (II; R = F, R′ = NO_2, R″ = Et) as another route to 4-fluoroindazole was unsuccessful.

In a second preparation of 5-fluoroindazole the nitration products of *m*-fluorotoluene were reduced and benzoylated. From the isomeric mixture of benzoyl compounds *N*-(4-fluoro-*o*-tolyl)benzamide was readily separable because of its insolubility in ethanol. Cyclisation of its *N*-nitroso-compound yielded a mixture of 5-fluoroindazole and a fluorine-free substance which is under investigation.

6-Fluoroindazole was obtained in a similar way from *N*-(5-fluoro-*o*-tolyl)benzamide.

The preparation of 7-fluoroindazole involved nitration of 4-acetamido-2-nitrotoluene [3] (IV; R = R′ = H). Nitration with fuming nitric acid gave a 2 : 1 mixture of 4-acetamido-2,3- and 4-acetamido-2,5-dinitrotoluene. Dilution of the nitric acid reduced the proportion of the unwanted 2,5-dinitro-compound; nitric acid of sp. gr. 1·485 yielded 4-acetamido-2,3-dinitrotoluene as the sole product (Table 1). Interconversion of the isomeric compounds by migration of a nitro-group as recently described by Pausacker [5] was thought to be one of the reasons for this unusual result. However, migration could not be induced in these compounds under the conditions of nitration; only in sulphuric acid at 110° did 2,3- give 2,5-dinitro-*p*-toluidine. The presence of nitrous acid had a marked effect on the nitration (see Table).

TABLE 1. *Nitration of 4-acetamido-2-nitrotoluene.*

		Composition (%): [a]		
Sp. gr. of HNO_3	Yield (%)	2,3-Dinitro-*p*-toluidine	2,5-Dinitro-*p*-toluidine	Starting material (%)
1·500	86	70	30	—
1·485	60	100	—	—
1·475	19	100	—	—
1·460	—	—	—	100
1·500 [b]	33·5	33·5	—	66·5
1·485 [b]	—	—	—	100

[a] After hydrolysis. [b] Free from nitrous acid.

The position of entry of the nitro-group in the nitration of 4-acetamido-2-nitrotoluene must also be determined by the resultant electronic tendencies of the substituents, *i.e.*, a $+E$ group (NHAc) situated *meta* to a $-M$ group (NO_2). Such a situation has already been previously observed to favour nitration at a hindered position.[6]

The dinitro-compound (V; R = NO_2), whose structure follows from formation of the phenanthrazine (VI), was readily reduced with stannous chloride to the amine [7] (V; R = NH_2). A Balz–Schiemann reaction with the nitro-amine (V; R = NH_2) led to deamination. In view of this failure a recent method of introducing fluorine into aromatic compounds reported by Bergmann, Berkovic, and Ikan [8] in which a solution of a diazonium borofluoride in acetone is treated with copper powder or cuprous chloride was applied to 2-nitro-*m*-toluidine (V; R = NH_2). Again this gave deaminated products and we have shown elsewhere [9] that Bergmann's modification of the Balz–Schiemann reaction, although it generally fails to introduce fluorine, has preparative value as a deamination method.

5- and 6-Fluoroindazole proved ineffective on the Walker carcinoma 256 at a single dose of 25 mg. in oil per 200 g. rat.

EXPERIMENTAL

Diazonium borofluorides were decomposed in dry nitrogen.[10] Ultraviolet measurements (in methanol) were made with a Unicam S.P. 500 instrument and are quoted as $\lambda_{max.}$ in mμ, with $10^{-3}\varepsilon$ in parentheses.

[5] Pausacker and Scroggie, *J.*, 1955, 1897.
[6] Ingold, " Structure and Mechanism in Organic Chemistry," Bell and Sons, London, 1953, p. 268.
[7] Burton and Kenner, *J.*, 1921, **119**, 1047.
[8] Bergmann, Berkovic, and Ikan, *J. Amer. Chem. Soc.*, 1956, **78**, 6037.
[9] Barben and Suschitzky, *Chem. and Ind.*, 1957, 1039.
[10] Suschitzky, *J.*, 1953, 3042.

Nitroindazoles.—Diazotisation of the requisite nitro-*o*-toluidine in acetic acid according to the method used for 5-nitroindazole [1] was satisfactory.

Aminoindazoles.—The nitroindazoles were reduced with iron suspended in boiling water containing a little hydrochloric acid.[2] Some decompositions occurred in the case of the 4- and the 7-amino-compound. M. p.s agreed with the values in the literature.[3]

Monofluoroindazoles.—Method A. The aminoindazole (1 mol.) in hydrochloric acid (3·4 mols.) was diazotised below 0°. Addition of aqueous sodium borofluoride (1·2 mols.) precipitated the diazonium borofluoride which was washed with 10% aqueous sodium borofluoride solution and ether, dried, diluted with sand, and then decomposed. The monofluoroindazole was driven off by steam and extracted from the distillate with ether. 7-Aminoindazole had to be diazotised in 42% hydroborofluoric acid at −10°. Its diazonium compound contained a fluorine-free, solid impurity. The *compounds* thus prepared are listed in Table 2. Indazole-5-, -6-, and -7-diazonium borofluoride melted at 124—125°, 125—126°, 133—135°, respectively, all with decomp.

Ultraviolet absorptions of the fluoroindazoles were:

4-Fluoroindazole: 214(8·07), 247(3·99), 283(4·00), 294(2·92).

5-Fluoroindazole: 214(6·18), 248(5·0), 252(5·06), 291(4·8), 298(4·66), 300(3·83), 305(4·01).

6-Fluoroindazole: 213(9·14), 261(4·63), 279(4·72), 290(3·97).

7-Fluoroindazole: 212(6·8), 246(4·23), 283(3·73), 295(2·94).

Method B. A suspension of the *N*-fluorotolylbenzamide in acetic anhydride and acetic acid was nitrosated at 0—5° with nitrous fumes (generated by Bachmann's method [11]) for 1 hr. The nitroso-compound precipitated when the deep-green mixture was poured on ice, was collected, washed free from acid (ice-water), dried, and dissolved in benzene (sodium-dried). This mixture was set aside for 2 days and yielded the indazole on extraction with hydrochloric acid followed by basification of the acid extract.

Ethyl 4-fluoroindazole-6-carboxylate was obtained from the liquid nitroso-compound as needles (from water), m. p. 137° (Found: C, 57·9; H, 4·6. $C_{10}H_9O_2N_2F$ requires C, 57·7; H, 4·35%). Hydrolysis by 2N-sodium hydroxide gave the *acid* which, purified as its ammonium salt and recrystallised from nitromethane, had m. p. 306—310° (decomp.) dependent on the rate of heating (Found: equiv., 198. $C_8H_5O_2N_2F,H_2O$ requires equiv., 198).

5-Fluoroindazole. Cyclisation of N-(*4-fluoro-o-tolyl*)-N-*nitrosobenzamide*, m. p. 62—63° (decomp.) (Found: C, 64·9; H, 4·5; N, 10·9. $C_{14}H_{11}O_2N_2F$ requires C, 65·1; H, 4·5; N, 10·85%), gave 5-fluoroindazole, m. p. and mixed m. p. 121° with a sample prepared by method A.

TABLE 2. *Substituted indazoles.*

		Found (%)				Required (%)			Yield [a]
Subst.	M. p.	C	H	N	Formula	C	H	N	(%)
5-F	121°	61·8	3·9	20·5	$C_7H_5N_2F$	61·5	3·7	20·5	19
6-F	126	—	—	20·6					9
7-F	120	61·7	3·7	20·4					27

[a] Yields are based on diazonium borofluorides.

6-Fluoroindazole. The nitroso-compound obtained from *N*-(5-fluoro-*o*-tolyl)benzamide had m. p. 59° (decomp.) and cyclised readily to 6-fluoroindazole (62%), m. p. and mixed m. p. 125—126°. Its dry silver salt (prepared from aqueous solutions of the indazole and silver nitrate) with an excess of methyl iodide at room temperature afforded an oil which readily formed *6-fluoro-2-methylindazole picrate* as yellow needles, m. p. 166° (Found: C, 44·5; H, 2·8. $C_{14}H_{10}O_7N_5F$ requires C, 44·3; H, 2·7%).

*3,5-Dinitro-*p*-toluic Acid.*—This was made by addition of nitric acid (80 ml.; *d* 1·51) to a stirred solution of *p*-toluic acid (50 g.) in sulphuric acid (200 ml.; *d* 1·84) at 15—25° during 1·5 hr. After being heated on a water-bath for 2·5 hr., the mixture was poured on ice. 3,5-Dinitro-*p*-toluic acid (75 g., 86%) crystallised from ethyl acetate–light petroleum (b. p. 60—80°) as prismatic needles, m. p. 157°. Brückner [12] records m. p. 157—158°. Its *amide* was obtained as needles, m. p. 187° (Found: C, 42·6; H, 3·1. $C_8H_7O_5N_3$ requires C, 42·7; H, 3·1%). Its *ethyl ester*, prepared with ethanol and sulphuric acid, had m. p. 72—73° (Found: C, 47·6; H, 3·5. $C_{10}H_{10}O_6N_2$ requires C, 47·25; H, 4·0%).

[11] Bachman, "Organic Reactions," Wiley, 1944, Vol. II, 249.

[12] Brückner, *Ber.*, 1875, **8**, 1678.

3-*Amino-5-nitro*-p-*toluic Acid*.—Reduction of a boiling ethanolic solution of 3,5-dinitro-*p*-toluic acid with 8% aqueous ammonium sulphide (226 ml.) was complete in 2·5 hr. Filtration and acidification of the filtrate to pH 4 precipitated 3-amino-5-nitro-*p*-toluic acid as yellow needles (purified *via* its ammonium salt), m. p. 213°. Claus and Beysen [13] report m. p. 214°. Its *acetyl derivative* crystallised as needles, m. p. 242° (Found: C, 50·4; H, 4·2. $C_{10}H_{10}O_5N_2$ requires C, 50·4; H, 4·2%). The *ethyl ester* had m. p. 145° (Found: C, 53·8; H, 5·6. $C_{10}H_{12}O_4N_2$ requires C, 53·7; H, 5·4%). From the crude ester a small quantity of *ethyl* 3,5-*diamino*-p-*toluate* was separable by fractional crystallisation from benzene as blunt needles, m. p. 145—147° (Found: N, 14·2. $C_{10}H_{14}O_2N_2$ requires N, 14·4%). This compounds was prepared unambiguously by reduction of an ethanolic solution of the dinitro-ester with Raney nickel and hydrogen at atmospheric pressure.

3-*Fluoro-5-nitro*-p-*toluic Acid*.—The 3-amino-5-nitro-ester (15 g.) yielded a diazonium borofluoride (16·2 g., 75%), m. p. 128° (decomp.), which on dry decomposition gave pale-yellow needles of *ethyl* 3-*fluoro-5-nitro*-p-*toluate* (50%), m. p. 50°, purified by sublimation at 90°/30 mm. (Found: C, 52·9; H, 4·9. $C_{10}H_{10}O_4NF$ requires C, 52·9; H, 4·9%), hydrolysis of which yielded the *acid*, m. p. 160°, as needles (Found: C, 48·5; H, 3·3. $C_8H_6O_4NF$ requires C, 48·25; H, 3·0%).

N-(3-*Fluoro*-o-*tolyl*)*benzamide*.—3-Fluoro-5-nitro-*p*-toluic acid (0·5 g.) was decarboxylated in quinoline with a trace of copper bronze under reflux in 1·5 hr. Pouring the mixture into dilute hydrochloric acid followed by steam-distillation gave 2-fluoro-6-nitrotoluene (0·25 g.), which on reduction by stannous chloride and benzoylation gave the benzamide, m. p. and mixed m. p. 157—158° with a sample prepared by another method.[4]

Ethyl 3-*Benzamido-5-fluoro*-p-*toluate*.—By shaking an ethanolic solution of the fluoronitro-ester with Raney nickel under hydrogen an *amino-ester* was obtained as needles, m. p. 64° (Found: C, 61·2; H, 6·4. $C_{10}H_{12}O_2NF$ requires C, 60·9; H, 6·1%), which on benzoylation gave this *benzamido-ester*, m. p. 137°, as needles (Found: C, 67·5; H, 5·5. $C_{17}H_{16}O_3NF$ requires C, 67·8; H, 5·35%).

N-(4-*Fluoro*-o-*tolyl*)*benzamide*.—The mixture of products obtained on nitration of *m*-fluorotoluene [14] was reduced with iron and ammonium chloride solution and then benzoylated. The benzamide, m. p. 166° (lit.,[14] m. p. 166°), separated as the least soluble isomer from hot ethanol. The isomeric mixture of benzoates in the mother-liquor could not be separated by fractional crystallisation or chromatography.

N-5-(*Fluoro*-o-*tolyl*)*benzamide* was made by reduction (stannous chloride) of 4-fluoro-2-nitrotoluene followed by benzoylation. It had m. p. 117° (Found: C, 73·6; H, 4·9. $C_{14}H_{12}ONF$ requires C, 73·4; H, 5·2%).

Nitration of 4-*Acetamido-2-nitrotoluene*.—(*a*) Finely powdered 4-acetamido-2-nitrotoluene (5·0 g.) was added in 1·5 hr. to stirred nitric acid (165 ml.) at 0—1°, and the mixture was stirred for a further hour, then poured on ice (400 g.). A solid separated which was collected, washed free from acid, and dried.

(*b*) Nitration with nitric acid free from nitrous acid (prepared by the method of Hughes and Ingold [15]) was carried out as described under (*a*). No nitrous acid was detectable [16] during the reaction. The results of these nitrations are given in Table 1.

Separation of the Dinitro-amines.—Mixtures of 4-amino-2,3- and 4-amino-2,5-dinitrotoluene (obtained by hydrolysis of the above nitration products with 1 part of sulphuric acid and 5 parts of ethanol) were separated by chromatography on alumina, with benzene containing 1% of light petroleum (b. p. 60—80°) as eluant. The 2,5-dinitro-isomer, m. p. 183—185° (Morton and MacGookin [17] report m. p. 185°) was eluted before the 2,3-dinitro-amine, m. p. 120°.

Rearrangement of 2,3-*Dinitro*-p-*toluidine*.—The amine (0·5 g.) in sulphuric acid (2·5 ml.) was heated at 110° for 4 hr. The brown product (0·48 g.) obtained by pouring the mixture on ice was purified by chromatography on alumina with benzene as eluant and yielded 2,5- (70%) and 2,3-dinitro-*p*-toluidine (30%).

Attempts to prepare N-(6-*Fluoro*-o-*tolyl*)*benzamide*.—Deamination of 2,3-dinitro-*p*-toluidine by diazotisation followed by addition of ethanol [18] gave 2,3-dinitrotoluene (75%). Reduction

[13] Claus and Beysen, *Annalen*, 1891, **266**, 235.
[14] Schiemann, *Ber.*, 1929, **62**, 1799.
[15] Hughes, Ingold, *et al.*, *J.*, 1950, 2400.
[16] Feigl, " Qualitative Analysis by Spot Tests," Elsevier, 1947, p. 312.
[17] Morton and MacGookin, *J.*, 1934, 910.
[18] Crossley and Morrell, *J.*, 1911, **99**, 2349.

by stannous chloride gave 3-amino-2-nitrotoluene (55%), m. p. 105—107° (Burton and Kenner [7] give m. p. 108°). On reduction of this nitro-amine with zinc dust in acetic acid and addition of the mixture to a solution of phenanthraquinone in sodium hydrogen sulphate, *1-methylphenanthrazine* separated as needles, m. p. 223° (Found: C, 85·4; H, 5·3. $C_{21}H_{14}N_2$ requires C, 85·7; H, 4·8%). 2-Nitrotoluene-*m*-diazonium borofluoride, m. p. 136° (decomp.), yielded only fluorine-free products when decomposed in the usual way or when treated by Bergmann's method.[8,9]

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