4. *Monofluoroisoquinolines. Part I.*

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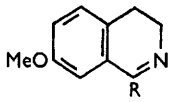
Seven fluorinated and three other 1-benzyl-3,4-dihydroisoquinolines are prepared by ring-closure from appropriate amides. Corresponding tetrahydroisoquinolines are also obtained. 8-Fluoroisoquinoline is described for the first time.

The only fluorine-containing isoquinolines so far reported are the 1-, 3-, 4-, and 5-monofluoroisoquinolines which were prepared [1] by the Balz–Schiemann reaction from the corresponding aminoisoquinolines; 1,3-difluoroisoquinoline which was obtained [2] by heating 1,3-dihydroxyisoquinoline with 2,4,6-trifluoro-1,3,5-triazine; and 6-fluoro-1,2,3,4-tetrahydro-2-thiocarbamoylisoquinoline.[3]

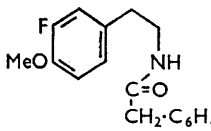
Cyclodehydration of *N*-acyl-2-arylethylamines to 3,4-dihydroisoquinolines, by treatment with reagents such as phosphorus oxychloride, phosphorus pentoxide, phosphorus pentachloride, polyphosphoric acid, or anhydrous zinc chloride (the Bischler–Napieralski reaction [4]), has now been successfully applied to the preparation of the monofluoro-1-benzyl-3,4-dihydroisoquinolines shown in Table 2. The best yields were obtained by heating the amide in boiling xylene with phosphorus pentoxide, and the standard time of 18 hours was adopted.

Ring-closure of *N*-phenylacetyl-3-fluorophenethylamine could yield either 1-benzyl-6- or 1-benzyl-8-fluoro-3,4-dihydroisoquinoline but, as expected,[4] the former resulted. This was proved by showing that the derived tetrahydroisoquinoline was different from 1-benzyl-8-fluoro-1,2,3,4-tetrahydro-2-methylisoquinoline, which was prepared from 8-fluoroisoquinolinium methiodide and benzylmagnesium chloride. 8-Fluoroisoquinoline has itself been prepared for the first time by the application of the Balz–Schiemann reaction to 8-aminoisoquinoline.

The 3,4-dihydroisoquinolines have been reduced to the 1,2,3,4-tetrahydro- and 1,2,3,4-tetrahydro-2-methyl derivatives (see Tables 3 and 4).



(I)



(II)

The generally accepted mechanism of the Bischler–Napieralski reaction [4,5] involves electrophilic attack on the aromatic nucleus on which ring closure is to occur. Thus, electron-releasing groups attached to this ring, especially if *ortho* or *para* to the position of ring-closure, would be expected to facilitate the reaction, and examples of successful ring-closures to activated aromatic nuclei are numerous.[4] Fluorine, like chlorine, exhibits

[1] Roe and Teague, *J. Amer. Chem. Soc.*, 1951, **73**, 687.
[2] B.P. 845,062/1960.
[3] Bloom, U.S.P. 2,899,426.
[4] Whaley and Govindachari, *Org. Reactions*, 1951, **6**, 74.
[5] Ritchie, *J. Proc. Roy. Soc. New South Wales*, 1945, **78**, 147.

electromeric control over such reactions as electrophilic aromatic substitution; the strong *ortho–para*-directing influence of fluorine is shown, for example, in the nitration of fluorobenzene which gives [6] a 76% yield of *p*-fluoronitrobenzene. The orienting effect of fluorine seems to be superior to that of a methyl group since nitration of *o*-fluorotoluene gives [7] an 84% yield of 2-fluoro-5-nitrotoluene, but inferior to that of a methoxyl group since nitration of *o*-fluoroanisole results [8] in a good yield of 2-fluoro-4-nitroanisole. The formation of the 5-, 6-, and 7-fluoro-3,4-dihydroisoquinolines in such high yields (Table 2) is in accord with the electromeric influence of the fluorine atom attached to an aromatic ring.

Ring-closure of *N*-phenylacetyl-4-fluorophenethylamine gives a 62% yield of the dihydroisoquinoline, and the analogous chloro- and bromo-amide give 72% yields. Attempted ring-closure of *N*-phenylacetyl-4-methoxyphenethylamine under the standard conditions gave only 0·4% of basic material, but 1-benzyl-3,4-dihydro-7-methoxyisoquinoline was obtained in 67% yield after 18 hours' heating with phosphorus pentoxide in benzene. Attempts [9] to cyclise *N*-acetyl-4-methoxyphenethylamine with phosphorus pentoxide at 207° is reported not to yield the isoquinoline derivative, and attempts to prepare compounds of the type (I) under our conditions also failed,[10] although a fair yield of (I; R = *p*-MeO·C_6H_4·CH_2) was obtained [10] by using phosphorus oxychloride under pressure. The amide (II) gave no basic material under the standard conditions but a 28% yield of the corresponding 3,4-dihydroisoquinoline with phosphorus pentoxide in benzene. The last result is somewhat surprising in view of the high yields of 6-fluoro- and 7-methoxy-bases described above.

Experimental

Monofluorobenzyl cyanides [11] were prepared by the action of *N*-bromosuccinimide on the corresponding fluorotoluenes (cf. Berger [12]), followed by treatment with sodium cyanide in dimethyl sulphoxide.[13]

Monofluorophenylacetic acids were obtained by the acid hydrolysis of the cyanides, as previously described.[11]

Monofluorophenethylamines.—A solution of the fluorobenzyl cyanide (40 g.) in dry benzene (25 ml.) was added in 45 min. to a stirred slurry of lithium aluminium hydride (20 g.) in anhydrous ether (300 ml.). The mixture was heated under reflux for 12 hr., with stirring, then cooled in ice whilst wet ether, and then water, were added. The resultant gelatinous precipitate was dissolved in hot 30% sulphuric acid (250 ml.); the mixture was cooled and sodium potassium tartrate (250 g.) in water (350 ml.) was added. The resultant solution was made alkaline with 30% aqueous sodium hydroxide and extracted with ether (1 l., total). The ethereal solution was dried and evaporated, and the residual oil was distilled under reduced pressure to yield the pure fluorophenethylamine in about 50% yield.

The same method was used to prepare 4-chloro-, 4-bromo-, and 3-fluoro-4-methoxy-phenethylamine. 4-Methoxyphenethylamine was obtained by reduction of the corresponding ω-nitrostyrene with lithium aluminium hydride.

N-*Arylacetyl*-2-*arylethylamines.*—A solution of the arylacetyl chloride (0·0575 mole) in dry benzene (30 ml.) was added dropwise to a stirred, ice-cold solution of the arylethylamine (0·115 mole) in benzene (30 ml.). The mixture was warmed on the water-bath for 30 min., then cooled, and the arylethylamine hydrochloride was filtered off and washed with benzene. The filtrate and washings were washed with 0·01N-sodium hydroxide (5 ml.) and with water (20 ml.), then dried and evaporated. The pale brown residual solid crystallised from light petroleum (b. p. 60—80°) or light petroleum–benzene. The *amides*, reported in Table 1, were obtained in 80—90% yield as colourless needles.

[6] Oláh, Pavláth, Kuhn, and Varsányi, *Acta Acad. Sci. Hung.*, 1955, **7**, 431.
[7] Suschitzky, *J.*, 1955, 4026.
[8] Schiemann and Miau, *Ber.*, 1933, **66**, 179.
[9] Moore, Weston, Sommers, Wright, Vernstein, Michaels, Denet, Freifelder, and Matson, personal communication quoted in ref. 4.
[10] Battersby and Ramuz, personal communication.
[11] Oláh, Pavláth, Oláh, and Herr, *J. Org. Chem.*, 1957, **22**, 879.
[12] Berger, Jacobson, and Kondritzer, *J. Org. Chem.*, 1957, **22**, 451.
[13] Friedman and Shechter, *J. Org. Chem.*, 1960, **25**, 877.

TABLE 1.

Substituted *N*-phenylacetylphenethylamines.

Substituent *	M. p.	Found (%) C	H	N	Hal	Formula	Required (%) C	H	N	Hal
2-Fluoro	92—93°	74·7	6·3	5·4	7·5					
3-Fluoro	72—73	74·8	6·4	5·4	7·2					
4-Fluoro	70—71	74·9	6·3	5·3	7·4					
2′-Fluoro	100—100·5	74·7	6·3	5·4	7·2	$C_{16}H_{16}FNO$	74·7	6·3	5·4	7·4
3′-Fluoro	67—68	74·8	6·4	5·4	7·4					
4′-Fluoro	90—91	74·7	6·3	5·5	7·4					
4-Chloro	104·5—105·5	70·7	5·9	5·2	(12·85 †)	$C_{16}H_{16}ClNO$	70·2	5·9	5·1	(12·95 †)
4-Bromo	132·5—134	60·7	5·2	4·4	(25·2 ‡)	$C_{16}H_{16}BrNO$	60·4	5·1	4·4	(25·1 ‡)
4-Methoxy	102·5—105	75·8	7·1	5·1	—	$C_{17}H_{19}NO_2$	75·8	7·1	5·2	—
3-Fluoro-4,3′,4′-trimethoxy ...	116—118·5	65·5	6·55	4·3	5·9	$C_{19}H_{22}FNO_4$	65·7	6·4	4·0	5·5

* Substituents in the acyl group are primed. † Cl. ‡ Br.

1-*Benzyl*-3,4-*dihydroisoquinolines: Standard Procedure.*—A mixture of the *N*-arylacetyl-2-arylethylamine (5·4 g.), xylene (190 ml.), powdered pumice (40 g.), and phosphorus pentoxide (80 g.) was heated under reflux with stirring for 18 hr. After cooling, the mixture was poured on ice (70 g.), and concentrated hydrochloric acid (30 ml.) was added. After brief warming to 80°, the mixture was cooled and filtered. The xylene layer was extracted with 20% hydrochloric acid (3 × 25 ml.), and the residual pumice was also extracted with 20% hydrochloric acid. The combined acid solutions were washed with ether, and then covered with ether (150 ml.). The ice-cooled solvent mixture was basified with 30% sodium hydroxide solution. The layers were separated and the aqueous layer was extracted with ether (3 × 120; 2 × 50 ml.). The combined ether solutions were dried and evaporated to leave a brown oil, characterised as the 1-benzyl-3,4-dihydroisoquinolinium picrate. The *products* are listed in Table 2.

TABLE 2.

Substituted 1-benzyl-3,4-dihydroisoquinolines.

Substituent	Yield (%)	Picrate, m. p.	Found (%) for picrate C	H	N	Hal	Formula	Reqd. (%) for picrate C	H	N	Hal
5-Fluoro	58	166—167°	56·4	3·8	11·9	4·1					
6-Fluoro	81	154—156	56·3	3·7	11·9	3·9					
7-Fluoro	62	163—164	56·5	3·7	11·9	4·1					
2′-Fluoro	83	143—145	56·4	3·8	12·2	4·1	$C_{16}H_{14}FN,C_6H_3N_3O_7$	56·4	3·7	11·9	4·1
3′-Fluoro	91	205—207	56·45	3·7	11·9	3·9					
4′-Fluoro	89	185—187	56·3	3·75	11·8	4·0					
7-Chloro	72	168—180	54·7	3·5	11·5	7·7	$C_{16}H_{14}ClN,C_6H_3N_3O_7$	54·5	3·5	11·6	7·3
7-Bromo	72	190—191	50·0	3·4	10·8	15·3	$C_{16}H_{14}BrN,C_6H_3N_3O_7$	49·9	3·2	10·6	15·1
7-Methoxy	67 *	184—186	57·5	4·4	11·5	—	$C_{17}H_{17}NO,C_6H_3N_3O_7$	57·5	4·2	11·7	—
6-Fluoro-7,3′,4′-trimethoxy ...	28 * 63 †	184·5—185	53·7	4·25	10·1	3·5	$C_{19}H_{20}FNO_3,C_6H_3N_3O_7$	53·8	4·2	10·0	3·4

* Prep. in benzene (not xylene). † Prep. in conditions of Pictet and Finkelstein (*Ber.*, 1909, **42**, 1979) for dihydropapaverine.

1-*Benzyl*-1,2,3,4-*tetrahydroisoquinolines.*—The 1-benzyl-3,4-dihydroisoquinolinium chloride (from 3·0 g. of the free base) was dissolved in methanol (50 ml.) and water (5 ml.) and cooled in ice, and sodium borohydride (7·0 g.) was added, with swirling, in portions. After 2·5 hours' heating, the mixture was cooled, and water (170 ml.) was added, followed by sodium hydroxide (15 g.). The alkaline solution was extracted with chloroform (total 400 ml.), and the chloroform was dried and evaporated to leave a brown oil, which was distilled, in a nitrogen atmosphere, under reduced pressure. The resultant tetrahydroisoquinolines were characterised as *picrates*. The products are listed in Table 3.

8-*Aminoisoquinoline.*[14,15]—This was prepared from 5-chloro-8-nitroisoquinoline as described by Ahmad and Hey [14] and was obtained as greenish needles, m. p. 172—173·5° (lit.,[14] 173—174°). The monopicrate was obtained as yellow needles (from water), m. p. 244—245° (decomp.) with

[14] Ahmad and Hey, *J.*, 1961, 3882.

[15] Robinson, *J. Amer. Chem. Soc.*, 1947, **69**, 1944; Osborn and Schofield, *J.*, 1956, 4191; Andersag, *Med. Chem. Abhandl. med. Chem.*, 1934, **2**, 377.

TABLE 3.

1-Benzyl-monofluoro-1,2,3,4-tetrahydroisoquinolines.

Compound	Yield * (%)	Picrate, m. p.	Found (%) for picrate C	H	N	F	Formula	Reqd. (%) for picrate C	H	N	F
5-Fluoro ...	56	190—192°	56·2	4·2	12·0	4·1	$C_{16}H_{16}FN,C_6H_3N_3O_7$	56·2	4·1	11·9	4·0
6-Fluoro ...	65	160—163	56·35	4·2	11·8	4·2					
7-Fluoro ...	52	92—98 †	54·1	4·5	11·4	4·1 †	$C_{16}H_{18}FNO,C_6H_3N_3O_7$	54·1	4·3	11·5	3·9 †
2′-Fluoro ...	79	195—197	56·3	4·1	12·05	4·1	$C_{16}H_{16}FN,C_6H_3N_3O_7$	56·2	4·1	11·9	4·0
3′-Fluoro ...	83	183—185	56·3	4·2	11·9	4·2					
4′-Fluoro ...	66	230—233 ‡	61·9	4·9	14·0	3·8 ‡	$C_{16}H_{16}FN,C_{10}H_8N_4O_5$	61·8	4·8	13·9	3·8 ‡

* Based on the amide. † $+H_2O$. ‡ Picrolonate.

1-*Benzyl*-1,2,3,4-*tetrahydro*-2-*methylisoquinolines*.—These were prepared, as above, by reduction of the dihydroisoquinolinium methiodide with sodium borohydride, and were characterised as *picrates* (Table 4).

TABLE 4.

1-Benzyl-monofluoro-1,2,3,4-tetrahydro-2-methylisoquinolines.

Compound	Yield * (%)	Picrate, m. p.	Found (%) for picrate C	H	N	F	Formula	Reqd. (%) for picrate C	H	N	F
5-Fluoro ...	78	196—198°	57·15	4·6	11·55	4·0	$C_{17}H_{18}FN,C_6H_3N_3O_7$	57·0	4·4	11·6	3·9
6-Fluoro ...	86	178—180	57·2	4·5	11·7	3·8					
7-Fluoro ...	73	167—168·5	57·0	4·45	11·5	3·9					
2′-Fluoro ...	80	139—141	57·1	4·4	11·6	4·0					
3′-Fluoro ...	87	190—193	57·2	4·5	11·5	4·1					
4′-Fluoro ...	61	156—158	56·3	4·4	11·3	4·0					

* Based on the 1-benzyl-3,4-dihydroisoquinolinium methiodide.

previous shrinking and darkening [lit.,[14] 231—232° (decomp.) with previous shrinking and darkening] (Found: C, 48·2; H, 3·1; N, 19·0. Calc. for $C_9H_8N_2,C_6H_3N_3O_7$: C, 48·3; H, 3·0; N, 18·8%).

8-*Fluoroisoquinoline*.—8-Aminoisoquinoline (4·0 g.) was added to 40% fluoroboric acid (35 g.) at −78°. The temperature was maintained at −15° to −20° whilst a solution of sodium nitrite (2·3 g.) in water (5 ml.) was added dropwise with stirring. The mixture was allowed to warm slowly to −4° with stirring, then cooled to −15°, and the pale brown, solid diazonium fluoroborate was collected, washed several times with 1 : 1 ether–ethanol (cooled to −10°), and dried in a vacuum over calcium chloride. The yield of fluoroborate was 6·3 g. and the m. p. 121° (decomp.). The diazonium fluoroborate (2·88 g.) was heated cautiously: it decomposed smoothly to leave a reddish oil; this was dissolved in warm 10% hydrochloric acid, basified with 30% sodium hydroxide solution, and steam-distilled. The first 100 ml. of distillate were extracted with ether (5 × 60 ml.), and the ethereal solution was dried and evaporated to leave 8-*fluoroisoquinoline*. The fraction, b. p. 87—88°/4·0 mm., of this solidified (0·53 g., 28%). The *picrate* was obtained as golden-needles (from water), m. p. 200—201° (Found: C, 47·9; H, 2·4; N, 15·0; F, 5·05. $C_9H_6FN,C_6H_3N_3O_7$ requires C, 47·9; H, 2·4; N, 14·9; F, 5·05%).

1-*Benzyl*-8-*fluoro*-1,2,3,4-*tetrahydro*-2-*methylisoquinoline*.—A cold solution of benzylmagnesium chloride [16] (from 1·1 g. of magnesium) in ether (26 ml.) was added dropwise during 20 min. to a stirred suspension of 8-fluoroisoquinolinium methiodide (3·5 g.) in ether (15 ml.), in a nitrogen atmosphere, and cooled in ice–salt. The mixture was stirred for a further 15 min., then decomposed with an ice-cold saturated solution of ammonium chloride (70 ml.). After addition of 50% hydrochloric acid (30 ml.) and separation of the layers, the red-brown ethereal solution was exhaustively extracted with 50% hydrochloric acid. The combined acid extracts were neutralised with ammonia (*d* 0·880), and the mixture was extracted with ether (1 × 200 ml.; 2 × 100 ml.). The ethereal solution was dried and evaporated, to leave a red oil of (presumably) 1-benzyl-8-fluoro-1,2-dihydro-2-methylisoquinoline, but this was unstable and was reduced immediately [17] by 60% hydrochloric acid (60 ml.) and tin foil (1·2 g.). The mixture was heated under reflux for a total of 8 hr. Upon cooling an off-white semi-solid separated. The mixture was basified and extracted with ether (total 800 ml.); the ethereal solution was dried and evaporated and the residue was distilled in an atmosphere of nitrogen. The fraction

[16] Gilman, Zoellner, and Dickey, *J. Amer. Chem. Soc.*, 1929, **51**, 1576.
[17] Freund and Bode, *Ber.*, 1909, **42**, 1746.

of b. p. 136—148°/2·5—3·0 mm. was collected (2·41 g.). The *picrate* was obtained as golden needles, m. p. 174·5—175°, from aqueous ethanol (Found: C, 57·1; H, 4·55; N, 11·6; F, 3·9. $C_{17}H_{16}FN,C_6H_3N_3O_7$ requires C, 57·0; H, 4·4; N, 11·6; F, 3·9%).

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