Organic Fluorine Compounds. Part XXXVI.[1] Preparation of *N*-substituted Amides of α-Fluoroacids

By **Israel Shahak** and **Ernst D. Bergmann**, Department of Chemistry, Hebrew University, Jerusalem

N-substituted α-chloro-, α-bromo- and α-toluene-*p*-sulphonyloxy-amides are converted into the corresponding α-fluoro-amides by reaction with potassium fluoride in bis(2-hydroxyethyl) ether.

THE simplest method for the preparation of α-fluoroacids, the reaction of α-chloroacid esters with potassium fluoride in acetamide with continuous removal of the α-fluoroester formed,[2,3] is not applicable to the esters of the higher α-chloroacids, since the product cannot be distilled off and is attacked by the acetamide, to give high-boiling material. Hoffman's[4] method which uses bis(2-hydroxyethyl) ether as a solvent for the metathetical reaction, is not applicable to the alkyl esters of α-haloacids since they undergo immediate ester exchange, and no fluorination takes place.

Since amides are much more stable to attack by bis-(2-hydroxyethyl) ether, the reaction of α-haloamides with potassium fluoride in this as a solvent has been studied. In order to facilitate the isolation of the products, *N*-substituted amides were employed which are easily soluble in organic solvents, such as benzene. It was found that α-chloro-, α-bromo-, and α-toluene-*p*-sulphonyloxy-amides are easily transformed into the analogous α-fluoroamides; anilides, benzoyl-substituted anilides, and *NN*-diethylamides have been used with good results. Recently, two patents[5] have described the analogous preparation of fluoroacetanilides, using nonylphenol–ethylene oxide copolymer or xylene as the reaction media. In this connection, it is recalled that Phillips[6] prepared fluoroacetamide by the reaction of chloroacetamide with potassium fluoride in xylene.

Bis(2-hydroxyethyl)ether has the advantage that potassium fluoride is soluble in it (to the extent of about 15%); the only side reaction is the replacement of the α-substituent by the $\cdot O\cdot(CH_2)_2\cdot O\cdot(CH_2)\cdot OH$ radical. This reaction does not constitute a major obstacle, however, except in the case of α-halophenylacetanilides, in which the yields are lower than for α-haloanilides of aliphatic acids. It may be worthwhile to point out that the type of reaction observed by Maynard[7] for aliphatic polychloro-compounds does not apply here; we believe that the metathetical reaction described here involves a nucleophilic attack on the C–Cl, C–Br, or $C-O-SO_2C_6H_5Me$ bond. In particular, the formation of the known α-fluoropropananilide from both α-chloro- and α-toluene-*p*-sulphonyloxypropananilide proves that the same mechanism operates for both reactions and

---

[1] Part XXXV, E. D. Bergmann and I. Shahak, *J. Chem. Soc.* (*C*), 1966, 899.

[2] E. D. Bergmann and I. Blank, *J. Chem. Soc.*, 1953, 3786.

[3] E. D. Bergmann and A. Cohen, *Tetrahedron Letters*, 1965, 1151.

[4] F. Hoffman, *J. Amer. Chem. Soc.*, 1948, **70**, 2596.

[5] Daikin Kogyo Co., F.P. 1,407,707 and 1,405,502 (*Chem. Abs.*, 1965, **63**, 13,164). Neth. P. 292,686 (*Chem. Abs.*, 1966, **64**, 2022. Neth. P. 6,500,874 (*Chem. Abs.*, 1966, **64**, 7982).

[6] M. A. Phillips, *Ind. Chemist*, 1954, **30**, 122.

[7] J. T. Maynard, *J. Org. Chem.*, 1963, **28**, 112.

that in neither of them is there an elimination of HX with subsequent addition of HF to the acrylanilide formed, since this sequence would give β-fluoropropananilide.

EXPERIMENTAL

(Note: It should be remembered that derivatives of fluoroacetic acid are toxic.)

A stirred mixture of the α-haloamide (0·1 mole), dry potassium fluoride (15 g., 0·25 mole), and bis(2-hydroxyethyl)ether (100 ml.) was heated rapidly to 125—130° and kept at this temperature for 2 hr. The product was cooled, diluted with water (200 ml.), and extracted with benzene (3 × 150 ml.). The benzene layer was washed with 5% sodium hydrogen carbonate solution (100 ml.), dried, and concentrated.

Starting material	Product (% yield)	B. p. (mm.)	M. p.	Remarks
Chloroacetanilide	$FCH_2 \cdot CO \cdot NHPh$ (65)	131—133°/1	76° [a]	(Found: F, 12·1. Calc. for C_8H_8FNO: F, 12·4%)
Bromoacetanilide	$FCH_2 \cdot CO \cdot NHPh$ (45)	131—133/1	76	
Toluene-*p*-sulphonoxyacetanilide	$FCH_2 \cdot CO \cdot NH \cdot Ph$ (54)	131—133/1	76	
Chloroacet-*p*-chloroanilide	$FCH_2CO \cdot NH \cdot C_6H_4 \cdot Cl$-*p* (53)		132 [b]	Recryst. from benzene–light petroleum (Found: C, 51·3; H, 3·8; N, 7·4; F, 10·4. Calc. for C_8H_7ClFNO: C, 51·1; H, 3·7; N, 7·4; F, 10·1%)
α-Chloropropananilide	$MeCHF \cdot CO \cdot NH \cdot Ph$ (64)		62 [c]	(Found: F, 11·8. Calc. for $C_9H_{10}FNO$: F, 11·4%)
α-Toluene-*p*-sulphonoxypropananilide	$MeCHF \cdot CO \cdot NH \cdot Ph$ (63)		62	
α-Bromobutananilide	$MeCH_2 \cdot CHF \cdot CO \cdot NH \cdot Ph$ [d] (66)	140—142/1	55	Recryst. from light petroleum (Found: C, 66·2; H, 6·5; F, 10·8. $C_{10}H_{12}FNO$ requires C, 66·7; H, 8·1; F, 10·6%)
α-Bromovaleroyl-*N*,*N*-diethylamide	$Me(CH_2)_2 \cdot CHF \cdot CO \cdot NEt_2$ [d] (69)	132—134/25		(Found: F, 10·5; N, 7·7. $C_9H_{18}FNO$ requires: F, 10·9; N, 8·0%)
α-Bromoheptananilide	$Me(CH_2)_4 \cdot CHF \cdot CO \cdot NH \cdot C_6H_5$ [d] (61)	136—138/1	56—57	Recryst. from light petroleum (Found: F, 8·2. $C_{13}H_{18}FNO$ requires F, 8·5%)
α-Bromoheptan-*p*-toluidide	$Me \cdot [CH_2]_4 \cdot CHF \cdot CO \cdot NH \cdot C_6H_4Me$-*p* [d] (62)	145—146/1	71	Recryst. from benzene–light petroleum (Found: F, 8·1. $C_{14}H_{20}FNO$ requires F, 8·0%)
α-Chlorophenylacetanilide	$PhCHF \cdot CO \cdot NHPh$ [d] (25)	174—175/1	103	Recryst. from aqueous isopropyl alcohol. (Found: F, 8·1. $C_{14}H_{12}FNO$ requires F, 8·3%)
α-Bromophenylacetanilide	$PhCHF \cdot CO \cdot NHPh$ (32)	174—175/1	103	

[a] H. Kituro *et al.*, *Chem. Abs.*, 1956, **50**, 3293, give m. p. 76—77°. [b] Ref. *a* give m. p. 132°. [c] Ref. *a* give m. p. 62°. [d] New compound.

For the α-toluene-*p*-sulphonyloxyamides the temperature of the reaction was 95—100° and the reaction time 40 min.

Starting Materials.—Bromoacetanilide,[8] m. p. 130°. Chloroacet-*p*-chloroanilide,[9] m. p. 168°. α-Chloropropananilide,[10] m. p. 92°. α-Bromobutananilide, m. p. 98°.[11] α-*Bromovaleroyl*-NN-*diethylamide*, from α-bromovaleroyl bromide[12] and diethylamine in benzene, b. p. 121—123° (0·5 mm.) (Found: Br, 34·2. $C_9H_{18}BrNO$ requires Br, 33·9%). α-*Bromoheptanilide*, from α-bromoheptanoyl bromide[12] and aniline in benzene; m. p. 62—63°, after recrystallisation from light petroleum (Found: Br, 28·1. $C_{13}H_{18}BrNO$ requires Br, 28·2%).

α-*Bromoheptan-p-toluidide*, from benzene–light petroleum, m. p. 79—80° (Found: Br, 26·7. $C_{14}H_{10}BrNO$ requires Br, 26·8%).

Toluene-p-sulphonyloxyacetanilide.—Toluene-*p*-sulphonyl chloride (57 g.) and pyridine (47·5 g.) were added to a solution of hydroxyacetanilide (45·3 g.) in benzene (300 ml.). The temperature was kept below 20° for 1 hr. and then set aside at room temperature for 48 hr. The mixture was poured into hydrochloric acid and the organic layer washed, dried, and evaporated. The *residue*, after recrystallisation from ethanol, melted at 144—145° (Found: C, 58·8; H, 5·1; S, 10·2. $C_{15}H_{15}NO_4S$ requires C, 59·0; H, 5·0; S, 10·5%).

α-*Toluene-p-sulphonyloxypropananilide* was prepared analogously from α-hydroxypropananilide, m. p. 132°. The compound had been prepared before[13] by a different route.

The results of the experiments are summarised in the Table.

[6/346 *Received, March* 17*th*, 1966]

---

[8] W. Flimm, *Ber.*, 1890, **23**, 58.

[9] A. Collet, *Bull. Soc. chim. France*, [3], 1902, **27**, 541.

[10] C. A. Bischoff and P. Walden, *Annalen*, 1894, **279**, 792.

[11] A. Tigerstedt, *Ber.*, 1892, **25**, 2924.

[12] S. M. Birnbaum, S. C. J. Fu, and J. P. Greenstein, *J. Biol. Chem.*, 1953, **203**, 378.

[13] C. M. Beans, J. Kenyon, and A. Phillips, *J. Chem. Soc.*, 1936, 303.