Reaction of Diazomethane with Quaternary Nitrogen Compounds to form Betaines

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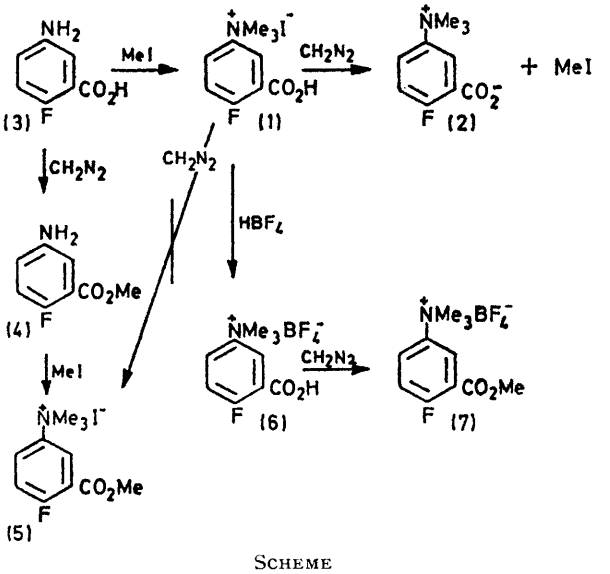
The reaction of diazomethane with 3-carboxy-4-fluorophenyltrimethylammonium iodide (1) affords, not the methyl ester, but the betaine 2-fluoro-5-trimethylammoniobenzoate (2). However, when the iodide anion is replaced by a weaker nucleophile, tetrafluoroborate, the methyl ester is obtained. A mechanism for the betaine reaction is outlined.

In our structural studies on insulin, activated fluorobenzenes containing a hydrophilic substituent have been used for chemical modification of the protein.[1] Such



Scheme

an intermediate, 3-carboxy-4-fluorophenyltrimethylammonium iodide (1) failed to undergo methylation to the required methyl ester with diazomethane. Instead, it yielded the betaine (2) and methyl iodide. Since this reaction may have some synthetic utility it was investigated in more detail.

Its closest analogy is a general method for the preparation of betaines from phenolic compounds bearing a quaternary nitrogen substituent.[2] In this case the reagent is aqueous potassium carbonate. Considerable information is also available on the action of diazomethane on compounds bearing only the quaternary nitrogen function. Müller and his co-workers [3] showed that in these cases the following reaction ensued: $R_2\overset{+}{N}H{\cdot}CH_3 + CH_2N_2 \longrightarrow R_2\overset{+}{N}(CH_3)_2 + N_2$. This was always the case provided that the anion of the salt was a poor nucleophile and did not itself react with the diazomethane. Thus, by using tetrafluoroborate salts these workers obtained reasonable yields of quaternary dimethylammonium salts. In good agreement with these generalisations are the findings of Daniels and Kormendy,[4] who, stimulated by the work of King and Miller [5] on six-membered aromatic heterocycles, showed that in pyridinium tetrafluoroborate, for example, a proton was first transferred from the pyridinium ion to the diazomethane; the resultant methanediazonium ion then attacked the free base to yield the *N*-methyl derivative and nitrogen.

With the above observations in mind we carried out

[1] D. A. Sutton, S. E. Drewes, and U. Welz, *Biochem. J.*, 1972, **130**, 589.
[2] J. P. Saxema, *J. Sci. Ind. Res., India*, 1963, **22**, 81.
[3] E. Müller, H. Huber-Emden, and W. Rundel, *Annalen*, 1959, **623**, 34.
[4] R. Daniels and C. K. Kormendy, *J. Org. Chem.*, 1962, **27**, 1860.
[5] L. C. King and F. M. Miller, *J. Amer. Chem. Soc.*, 1948, **70**, 4154.

the transformations shown in the Scheme. The results showed that the conversion (1) ⟶ (5) could not be achieved by direct reaction with diazomethane: this reaction leads to the betaine (2). To obtain the ester (5) a longer route had to be followed involving compounds (3) and (4). Under the anhydrous conditions of reaction no methylation of the amine [6] occurred during the conversion (3) ⟶ (4). Also, replacement of the strongly nucleophilic iodide anion by the weakly nucleophilic tetrafluoroborate anion in (1) to give (6) changed the course of the diazomethane reaction as predicted by Müller.[3] The ester (7) could then be obtained from (6) and no betaine was formed. These reactions lead us to suggest a mechanism which involves initial nucleophilic attack of the diazomethane on the carboxy-group, followed by preferential reaction of the resulting methanediazonium cation with iodide anion. By contrast, when tetrafluoroborate is the anion, reaction with the carboxylate anion is preferred, with formation of the ester. The alternative unimolecular decomposition of the methanediazonium ion (Me^+N_2 ⟶ $Me^+ + N_2$ ⟶ MeI) cannot be excluded but is considered to be less likely.

N.m.r. and Mass Spectra.—The n.m.r. spectra of all the quaternary amines and the betaine (2) were recorded with D_2O or trifluoroacetic acid as solvent. In all cases the aromatic protons resonated as a multiplet between δ 6·5 and 8·5. Typically the Me_3N^+ signal appeared as a singlet at about δ 3·3.

The mass spectra of the quaternary salts (1), (5), (6), and (7) differed markedly from that of the betaine (2). Whereas the betaine had as its base peak the molecular ion, this peak was entirely absent in the spectra of the four quaternary salts. The two iodides (1) and (5) decomposed thermally, as anticipated,[7] to yield the tertiary amine (base peak) and methyl iodide. For the tetrafluoroborate salts (6) and (7) the base peak occurred at $M^{+\cdot} - (CH_3\cdot + HBF_4)$ with the next most intense peak at $M^{+\cdot} - (CH_3\cdot + BF_4^-)$. These two salts illustrate the effect of the anion on the fragmentation pattern.[8,9]

Although a large number of fluorobenzene derivatives are known, none of the relatively simple compounds shown in the Scheme appear to have been recorded previously.

EXPERIMENTAL

N.m.r. spectra were obtained with a Varian T60 spectrometer, and mass spectra with a Varian CH 7 instrument operating at 70 eV. Diazomethane was prepared by the method of de Boer and Backer.[10]

5-Amino-2-fluorobenzoic Acid (3).—Nitration of 2-fluorobenzoic acid [11] followed by reduction of the product with tin and hydrochloric acid gave the amino-acid as yellow *needles* (from water), m.p. 190° [Found: C, 48·5; H, 4·65; N, 8·0; H_2O (loss at 100 °C), 12·4. $C_7H_6FNO_2,H_2O$ requires C, 48·5; H, 4·65; N, 8·1; H_2O, 10·4%). The *acetate* had m.p. 256—258° (decomp.).

Methyl 5-Amino-2-fluorobenzoate (4).—Treatment of the acid (3) (0·5 g) in methanol at −10 °C with diazomethane gave pale yellow *needles* (0·7 g) (from tetrachloromethane), m.p. 86° (Found: C, 56·5; H, 4·4; N, 8·1. $C_8H_8FNO_2$ requires C, 56·8; H, 4·75; N, 8·3%), δ 3·9 (3H, s).

4-Fluoro-3-methoxycarbonylphenyltrimethylammonium Iodide (5).—Quaternisation of the amino-ester (4) (0·3 g) by the method of Sommer and his co-workers [12] with *NN*-diethylaniline (0·6 ml) as proton-acceptor base gave white *needles* (0·5 g), m.p. 205—207° (decomp.) (from methanol–acetone) (Found: C, 39·6; H, 4·3. $C_{11}H_{15}FINO_2$ requires C, 38·9; H, 4·45%).

3-Carboxy-4-fluorophenyltrimethylammonium Iodide (1).—The acid (3) (1·8 g) in dimethylformamide (2 ml) was quaternised as before to give white *needles* (2·3 g), m.p. 165° (from dimethylformamide–acetone) (Found: C, 37·4; H, 4·4. $C_{10}H_{13}FINO_2$ requires C, 36·9; H, 4·05%). Methylation of (1) with diazomethane (−10 °C in MeOH) did not yield the ester (5), although the latter is stable under these conditions.

2-Fluoro-5-trimethylammoniobenzoate (2).—The iodide (1) (0·6 g) was methylated with diazomethane at −10° to give white *plates* (0·2 g), m.p. 250° (from methanol–acetone) [Found: C, 51·2; H, 6·75; N, 5·7; H_2O (loss at 150 °C), 14·1. $C_{10}H_{12}FNO_2,2H_2O$ requires C, 51·5; H, 6·9; N, 6·0; H_2O, 15·4%). The methyl iodide evolved was measured quantitatively by the standard Zeisel procedure.

3-Carboxy-4-fluorophenyltrimethylammonium Tetrafluoroborate (6).—To the iodide (1) (0·4 g) in methanol, fluoroboric acid (3 ml) was added. The solvent was removed *in vacuo*, the residue dissolved in acetone, and the *product* (0·2 g) precipitated with ether; m.p. 196—200° (decomp.) (Found: C, 42·0; H, 5·15. $C_{10}H_{13}BF_5NO_2$ requires C, 42·1; H, 5·6%).

4-Fluoro-3-methoxycarbonylphenyltrimethylammonium Tetrafluoroborate (7).—The acid (6) (0·2 g) was methylated at −10 °C as before to yield white *needles* (0·2 g), m.p. 208—211° (decomp.) (from methanol–acetone–ether) (Found: C, 43·9; H, 5·15. $C_{11}H_{15}BF_5NO_2$ requires C, 44·1; H, 5·05%).

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