# THE SYNTHESIS OF *ORTHO*-SUBSTITUTED 2-DIETHYLAMINOETHYL BENZOATES AS POTENTIAL LOCAL ANAESTHETICS

BY J. THOMAS AND J. CANTY

*From The Department of Pharmacy, University of Manchester*

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A series of mono-*ortho*- and di-*ortho*- substituted benzoic esters of 2-diethylaminoethanol has been synthesised. Improved methods for the preparation of 2,6-difluorobenzoic acid and 2,6-dimethylbenzoic acid are reported. The preparation of esters of di-*ortho*- substituted benzoic acids is discussed and an efficient method of esterification of these acids is described.

THOMAS and Stoker (1961) demonstrated that *ortho* substitution in benzoylcholine could lead to increased stability of the ester group towards both hydroxide-ion- and cholinesterase-catalysed hydrolysis and that the *ortho* substituents did not prevent the formation of an enzyme–substrate complex. Two enzymes, acetylcholinesterase and cholinesterase, were used. Thomas and Buckley (1962) examined the effects of *ortho* substitution in benzoylcholine on some of the pharmacological actions of the ester. Neuromuscular block of the rat diaphragm–phrenic nerve preparation and stimulation of the frog rectus abdominis preparation were examined. It was found that *ortho* substitution did not necessarily reduce the activity from that of benzoylcholine and in some instances an increase in potency was noted. The conclusion from these studies is that *ortho* substitution of benzoic esters is, in principle at least, a method of decreasing the rate of both *in vivo* and *in vitro* hydrolysis of the ester group without removing the biological actions of such esters.

To examine a further application of *ortho* substitution of benzoic esters in medicinal chemistry a series of mono-*ortho*- and di-*ortho*-substituted 2-diethylaminoethyl benzoates has now been synthesised for testing for their ability to block axonal nervous transmission.

A number of *ortho*-substituted benzoic esters with local anaesthetic activity have been reported. Dvoretzky and Richter (1953) prepared ethyl and propyl 4-amino-2,6-dimethylbenzoate and reported them to have a longer duration of local anaesthetic action than benzocaine. They postulated that this was due to the decreased rate of hydrolysis. Childress and others (1954) reported that 2-diethylaminoethyl 4-amino-2,6-dichlorobenzoate had an intradermal local anaesthetic activity 3·5 times as great as procaine, and that the duration of action was considerably longer. Rabjohn and others (1955) prepared a number of 2-diethylaminoethyl esters of sterically hindered alkyl-substituted benzoic acids and found them to show considerably longer duration of anaesthetic action than equipotent concentrations of procaine. Mono-*ortho*-substituted benzoic esters with local anaesthetic activity have also been examined. Foldes and Rhodes (1953) have reported that chloroprocaine is an excellent local anaesthetic. A wider range than previously reported of both mono-*ortho*

and di-*ortho*-substituted benzoic esters with local anaesthetic activity has now been prepared.

## EXPERIMENTAL

### *Mono*-ortho-*Substituted esters*

All the mono-*ortho*-substituted benzoic acids and some of the acid chlorides were obtained commercially. The method used to prepare 2-diethylaminoethyl *o*-methoxybenzoate is typical of the general method used to prepare the mono-substituted esters.

o-*Methoxybenzoyl chloride.* *o*-Methoxybenzoic acid (15·2 g. 0·1 mole) was refluxed with thionyl chloride (11·9 g. 0·1 mole) in a 50-ml. flask on a steam-bath for 2 hr. after which no further fumes of hydrogen chloride were evolved. The reaction mixture was distilled under reduced pressure and *o*-methoxybenzoyl chloride was collected as a colourless liquid, b.p. 131° at 12 mm. Yield 15 g.

2-*Diethylaminoethyl* o-*methoxybenzoate hydrochloride.* *o*-Methoxybenzoyl chloride (5·5 g. 0·05 mole) was dissolved in dry benzene (25 ml.) in a 100-ml. two-necked flask fitted with a reflux condenser and a dropping funnel. The mixture was refluxed and 2-diethylaminoethanol (5·8 g. 0·05 mole) was added dropwise over 30 min. The mixture was refluxed for a further 1 hr. and the contents allowed to cool. The precipitate was filtered, washed with dry benzene, dried, and recrystallised from an acetone-ethanol mixture to give a white crystalline solid, m.p. 136°. Yield 55 per cent. $C_{14}H_{22}ClNO_3$ requires: C, 58·4; H, 7·7; Cl, 12·35. Found: C, 58·28; H, 7·9; $Cl^-$, 12·36.

A list of mono-*ortho*-substituted compounds prepared by this method and details of the preparation of each are given in Table I.

TABLE I

MONO-ORTHO-SUBSTITUTED 2-DIETHYLAMINOETHYL BENZOATE HYDROCHLORIDES

| Compound | Acyl halides | | 2-diethylaminoethyl benzoates hydrochloride | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Analysis | | | | | |
| | | | | | | | Found | | | Required | | |
| 2-diethyl-aminoethyl X-benzoates X = | Reflux time hr. | b.p. | Reflux time hr. | Solv. for recryst. | m.p. °C | Yield per cent | C | H | Cl | C | H | Cl |
| *o*-Methyl | 1 | 87–8° at 15 mm. | 1½ | Acetone | 133–5 | 66 | 61·5 | 7·9 | 13·02 | 61·8 | 8·1 | 13·08 |
| *o*-Ethoxy | 2 | 130° at 27 mm. | 2 | Acetone-ethanol | 138 | 63 | 59·3 | 8·1 | 11·97 | 59·7 | 8·0 | 11·78 |
| *o*-Iodo | 2 | (*a*) | 1½ | Acetone-ethanol | 155 | 32 | 40·5 | 4·8 | 9·28 | 40·7 | 5·0 | 9·26 |
| *o*-Nitro | 1 | (*a*) | 1½ | Acetone-ethanol | 165 | 68 | 51·8 | 6·0 | 11·68 | 51·6 | 6·3 | 11·74 |
| *o*-Bromo | (*b*) | | 1½ | Acetone-ethanol | 130 | 67 | 46·2 | 6·1 | 10·71 | 46·4 | 5·7 | 10·56 |
| *o*-Chloro | (*b*) | | 1½ | Acetone-ethanol | 127–8 | 73 | 53·3 | 6·4 | 12·16 | 53·4 | 6·5 | 12·16 |
| | (*b*) | | 1½ | Acetone-ethanol | 123–4 | 63 | 60·3 | 7·7 | 13·92 | 60·5 | 7·8 | 13·80 |

(*a*) Not isolated. (*b*) Acyl chloride obtained commercially.

### *Di*-ortho-*Substituted Esters*

6-*Nitro*-o-*toluidine.* 2,6-Dinitrotoluene (50 g.) was dissolved in ethanol (100 ml. 95 per cent) in a 500-ml. three necked flask fitted with a reflux

condenser, mechanical stirrer and dropping funnel. The solution was stirred and refluxed while an ammonium sulphide solution (280 ml. 16 per cent) was added dropwise over 30 min., refluxed for a further 15 min. and then cooled. The buff coloured precipitate which appeared was filtered off, washed with water and transferred to a beaker containing hydrochloric acid (36 ml.) and water (300 ml.). The mixture was boiled, filtered hot and the residue extracted a second time with acid. The acidic filtrates were mixed and the 6-nitro-*o*-toluidine hydrochloride crystallised out overnight in a refrigerator. The free base was obtained by treating an aqueous solution of the salt with sodium bicarbonate, collecting the precipitate, washing it with water and drying the yellow product at 60°, m.p. 89–91° (Brady and Taylor, 1920; m.p. 91·5°). Yield 39·2 g. 94 per cent.

2-*Methyl*-3-*nitrobenzenediazonium fluoroborate.* 6-Nitro-*o*-toluidine (38 g.) was suspended in hydrochloric acid (60 ml.) in a 1 litre polythene beaker. An aqueous solution of sodium fluoroborate (65 g. in 50 ml.) was added and the mixture cooled to 0°. A cold (0°) aqueous solution of potassium nitrite (25 g. in 25 ml.) was added dropwise over 1 hr. while the mixture was stirred with a copper rod. The mixture was maintained at 0° for a further hr. to allow the diazotisation to go to completion and then cooled to −5° for another hr. to complete the precipitation of 2-methyl-3-nitrobenzenediazonium fluoroborate. The fawn-coloured product was filtered off on a sintered-glass filter and then washed in turn with (*a*) sodium fluoroborate solution (40 ml. 5 per cent), (*b*) ethanol (25 ml. 95 per cent) and (*c*) ether (2 × 50 ml.), the solid being sucked as dry as possible after each washing. The white product was dried at 40°. Yield 88 g.

2-*Fluoro*-6-*nitrotoluene.* 2-Methyl-3-nitrobenzenediazonium fluoroborate (78 g.) was mixed with an equal weight of pure dry sand and placed in a 500 ml. borosilicate round-bottomed flask. The flask was connected, by means of a glass tube (½ inch internal diameter) and a double-surface condenser, to two 250 ml. Erlenmeyer flasks which were cooled by a freezing mixture. The apparatus was evacuated and the diazonium compound heated gently to start decomposition. Heat was applied to maintain a steady rate of decomposition and finally the temperature of the mixture was raised to 300° to ensure complete reaction. The product, which was a brown oil, collected in the first Erlenmeyer flask and the fumes of boron trifluoride which were evolved were trapped in sodium hydroxide solution. Heating was stopped when fumes ceased to be produced. The distillate was washed in turn with sodium hydroxide solution (2 × 25 ml. 10 per cent) and water (2 × 25 ml.), then dried over calcium chloride and redistilled under reduced pressure to give a pale yellow oil, b.p. 209–210°, m.p. 6° (Lock, 1936; m.p. 6·7–7°). The presence of fluorine was established by a Lassaigne test. *Note:* When an attempt was made to decompose larger batches of 2-methyl-3-nitrobenzenediazonium fluoroborate (200 g.) an explosion occurred.

6-*Amino*-2-*fluorotoluene.* 2-Fluoro-6-nitrotoluene (31 g.) was treated portionwise with a solution of stannous chloride (152 g.) in hydrochloric

acid (160 ml.) in a 1-litre three-necked flask fitted with a mechanical stirrer, dropping funnel and reflux condenser. The fluoronitrotoluene, together with 50 ml. of the stannous chloride solution, was heated on a steam-bath and the mixture stirred continuously. The remainder of the stannous chloride solution was introduced in 20 ml. portions and the flask heated for a further 1 hr. after all the stannous chloride had been added. The reaction mixture was cooled, made alkaline with sodium hydroxide and then the free base steam-distilled off. The distillate was saturated with sodium chloride and extracted with ether. The ether was distilled off, the residue dried over sodium hydroxide and redistilled to give a pale brown oil, b.p. 204–5°. Yield 22·7 g., 91 per cent.

6-*Amino-2-fluorotoluene picrate* was prepared, m.p. 194–5°. $C_{13}H_{11}FN_4O_7$ requires: C, 44·1; H, 3·12. Found: C, 44·0; H, 3·2.

3-*Fluoro-2-methylbenzenediazonium fluoroborate.* This was prepared from 6-*amino-2-fluorotoluene* (31·2 g.) by the same method as was used for 2-methyl-3-nitrobenzenediazonium fluoroborate. Yield 67 g.

2,6-*Difluorotoluene.* This was prepared from 3-fluoro-2-methylbenzenediazonium fluoroborate (67 g.) by a similar method to that used for 2-fluoro-6-nitrotoluene, the only differences being that no sand was required as a diluent and decomposition occurred at 120–130°. The product was a colourless liquid, b.p. 114–115° (Lock, 1936; b.p. 112° corrected). Overall yield from 6-amino-2-fluorotoluene 34 per cent, $n_D^{20°}$, 1·4338.

2,6-*Difluorobenzoic acid.* This acid was prepared from 2,6-difluorotoluene (8·0 g.) by the method described for the preparation of 2,6-dichlorobenzoic acid from 2,6-dichlorotoluene by Norris and Bearse (1940). The product was crystallised from water, m.p. 155–6° (Lock, 1936; m.p. 157·5° corrected). Yield 6·1 g. 62 per cent. Found: C, 52·9; H, 2·7. Calc. for $C_7H_4F_2O_2$: C, 53·2; H, 2·5.

2,6-*Dinitrobenzoic acid.* This acid was prepared from 2,6-dinitrotoluene by oxidation with acid permanganate by the method described by Sirks (1908) but carrying out the reaction at 100°. The use of a higher temperature increased the yield. The product was crystallised from cold hydrochloric acid to give a white crystalline compound, m.p. 204–5° (Sirks; m.p. 201–3°). The yield based on the 2,6-dinitrotoluene consumed was 48 per cent. Found: C, 40·0; H, 2·2. Calc. for $C_7H_4N_2O_6$: C, 39·6; H, 1·89.

2,6-*Dimethylbenzoic acid.* 2-Iodo-*m*-xylene (14 g.), ethyl bromide (5·2 g.), magnesium turnings (10 g.), sodium-dried ether (15 ml.) and a small crystal of iodine were introduced into a two-necked 500 ml. flask which was fitted with a dropping funnel and reflux condenser, to both of which were attached calcium chloride guard tubes. The reaction commenced immediately and a solution of 2-iodo-*m*-xylene (27·4 g.) and ethyl bromide (12·8 g.) in dry ether (120 ml.) was run in over a period of 30 min. and then the mixture refluxed for a further 1 hr. The mixture was poured onto crushed solid carbon dioxide (80 g. approximately) in a beaker and stirred until the dry ice had evaporated. A mixture of crushed ice (200 g.) and dilute hydrochloric acid (60 ml.) was added with stirring and

the ether layer separated. The ethereal solution was washed with water (4 × 20 ml.) and then extracted with sodium hydroxide solution (2 × 50 ml. 5 per cent). The alkaline solution was decolourised with charcoal, acidified with hydrochloric acid and the precipitated 2,6-dimethylbenzoic acid filtered off. It was recrystallised from water, m.p. 115° (Jacobs and others, 1951; m.p. 115·5°). Yield 22·7 g. 91 per cent. Found: C, 71·96; H, 6·67. Calc. for $C_9H_{10}O_2$: C, 72·0; H, 6·65.

2,6-*Dichlorobenzoic acid.* This acid was prepared by the method of Norris and Bearse (1940), m.p. 143–4° (Norris and Bearse, 1940; m.p. 143°). Yield 12·8 g. 54 per cent. Found: C, 43·8; H, 2·4. Calc. for $C_7H_4Cl_2O_2$: C, 43·95; H, 2·1.

2,4,6-*Tribromobenzoic acid.* The acid was prepared from *m*-aminobenzoic acid by the method of Robinson and Robinson (1956), m.p. 192° (Robinson and Robinson, 1956; m.p. 192·5 to 194·5°). Found: C, 23·1; H, 0·80. Calc. for $C_7H_3Br_3O_2$: C, 23·42; H, 0·98.

2,6-Dimethoxybenzoic acid, 1-naphthoic acid and 2-naphthoic acid were obtained commercially.

2-*Diethylaminoethyl chloride hydrochloride.* 2-Diethylaminoethanol (58·5 g.) dissolved in dry benzene (750 ml.) was introduced into a 2-litre three-necked flask fitted with a reflux condenser, stirrer and a dropping funnel. The mixture was stirred and cooled while thionyl chloride (59·5 g.) was added dropwise over 2 hr. and then the mixture refluxed for 2 hr. The reaction mixture was cooled and the precipitate filtered off, washed with dry benzene, dried and recrystallised from an acetone-ethanol mixture, m.p. 211° (Slotta and Benisch, 1935; m.p. 212°). Yield 67 g. 78 per cent. Found: C, 41·9; H, 8·4; Cl, 20·75. Calc. for $C_6H_{15}Cl_2N$: C, 41·86; H, 8·7; $Cl^-$, 20·65.

2-*Diethylaminoethyl chloride.* 2-Diethylaminoethyl chloride hydrochloride (21·5 g.) was placed in a 500 ml. two-necked flask fitted with a vacuum-tight stirrer and a condenser set for distillation. Sodium hydroxide (10 g.) was ground to a fine powder, then added to the flask and mixed with the amine hydrochloride. The mixed powders were stirred and reduced pressure (50 mm.) applied to the apparatus. The flask was heated gently and a colourless liquid distilled over and was collected in a receiving flask cooled in an ice-bath. The product was dried over anhydrous magnesium sulphate in a refrigerator, filtered off and stored below 0°, b.p. 146° (Slotta and Benisch, 1935; b.p. 146–7°). Yield 13·5 g. 80 per cent.

The di-*ortho*-substituted esters were prepared by one of two methods:

*Method A*

2-*Diethylaminoethyl* 2,6-*dimethoxybenzoate hydrochloride.* 2,6-Dimethoxybenzoic acid (9·1 g.) and isopropanol (75 ml.) were introduced into a 250-ml. two-necked flask fitted with a reflux condenser and a dropping funnel. The solution was heated to 50° and 2-diethylaminoethyl chloride was added dropwise over 15 min. The reaction mixture was maintained at 50° for a further 15 min. and then refluxed for 12 hr.

The mixture was cooled to 0°, whereupon a buff coloured solid was precipitated, filtered off, washed with cold isopropanol and recrystallised from isopropanol, m.p. 186°. Yield 9·6 g. 60 per cent. $C_{15}H_{24}ClNO_4$ requires: C, 56·69; H, 7·6; Cl, 11·18. Found: C, 56·6; H, 7·6; Cl, 11·37.

*Method B*

2-*Diethylaminoethyl* 2,6-*difluorobenzoate hydrochloride.* This ester was prepared from 2,6-difluorobenzoic acid and 2-diethylaminoethyl chloride as described in Method A. However, as the ester did not crystallise readily from the reaction mixture, it was isolated in the following manner. The reaction mixture was evaporated to dryness under reduced pressure and the residue was dissolved in the minimum quantity of water, the solution made alkaline with sodium bicarbonate, and the free base which was liberated extracted with chloroform. The solution was dried with calcium chloride, the chloroform removed and the residue dissolved in dry benzene. Dry hydrogen chloride was passed through the solution and the resulting precipitate was filtered off, washed with benzene and recrystallised from an ethyl methyl ketone-ethanol mixture to give a white crystalline solid, m.p. 144°.

A list of di-*ortho*-substituted esters prepared by these two methods is given in Table II.

## Discussion

*Esterification of Di-*ortho*-Substituted Benzoic acids*

The general methods of esterification either fail or are very slow and produce poor yields with hindered acids such as di-*ortho*-substituted benzoic acids. Esterification by these methods involves an intermediate stage in which the acyl carbon atom has a tetrahedral configuration and the presence of two groups *ortho* to the carboxyl group restricts the space available for the formation of such a bulky intermediate. This is the primary steric effect of *ortho* substitutents and is the main reason why di-*ortho*-substituted benzoic esters are stable. (For a full discussion of the *ortho* effect see Stoker, 1959). In synthesising esters of di-*ortho*-substituted benzoic acids, therefore, a method of esterification which does not involve an attack on the acyl carbon atom is required. One such method which has been used is the silver salt method (Thomas and Stoker, 1961; Rabjohn and others, 1955.) The reactions involved in the preparation of amino-esters by this method are given in Fig. 1.

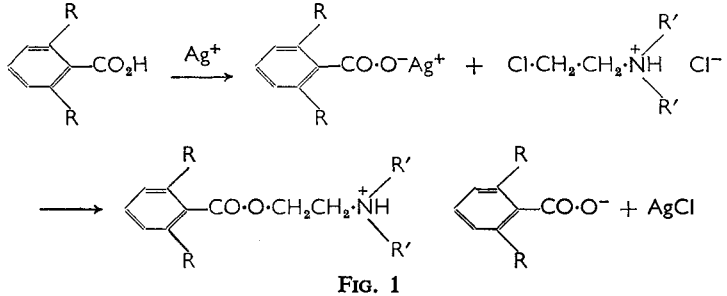


FIG. 1

TABLE II

DI-ORTHO-SUBSTITUTED BENZOIC AND 1- AND 2-NAPHTHOIC ESTERS OF 2-DIETHYL

| 2-Diethylaminoethyl hydrochloride ester of: | Method | Quantity of Reactants | | Reflux time hr. | Solv. for recryst. | m.p. °C | Yield per cent |
|---|---|---|---|---|---|---|---|
| | | Acid | Amino-chloride | | | | |
| 2,6-Difluorobenzoic acid .. | B | 3·16 g. 0·02 mole | 2·71 g. 0·02 mole | 7 | Ethyl methyl ketone | 144 | 55 |
| 2,6-Dichlorobenzoic acid .. | A | 9·55 g. 0·05 mole | 6·77 g. 0·05 mole | 10 | Isopropanol | 182 | 63 |
| 2,4,6-Tribromobenzoic acid .. | B | 3·59 g. 0·01 mole | 1·35 g. 0·01 mole | 8 | Acetone | 197–8 | 42 |
| 2,6-Dinitrobenzoic acid .. .. | A | 5·30 g. 0·025 mole | 3·39 g. 0·025 mole | 8 | Acetone | 158 | 62 |
| 2,6-Dimethylbenzoic acid .. | B | 3·75 g. 0·025 mole | 3·39 g. 0·025 mole | 8 | Ethyl methyl ketone | 164–5 | 56 |
| 2,6-Dimethoxybenzoic acid .. | A | 9·10 g. 0·05 mole | 6·77 g. 0·05 mole | 12 | Isopropanol | 186 | 60 |
| 1-Naphthoic acid .. .. | B | 6·90 g. 0·04 mole | 5·42 g. 0·04 mole | 10 | Acetone | 162–4 | 58 |
| 2-Naphthoic acid .. .. | B | 4·30 g. 0·025 mole | 3·39 g. 0·025 mole | 10 | Acetone | 163–4 | 62 |

The reaction is slow because it is heterogeneous. Other disadvantages of this method are that silver is expensive, and that the highest theoretical yield based on the acid is only 50 per cent since the insolubility of silver chloride causes one molecule of the acid to become the anion of the amino-ester salt.

A method of esterifying di-*ortho*-substituted benzoic acids has now been developed without the disadvantages of the silver salt method. It consists of reacting the acid with the alkylamine chloride (in the present case 2-diethylaminoethyl chloride) in a suitable solvent such as isopropanol. The reaction is given in Fig. 2.

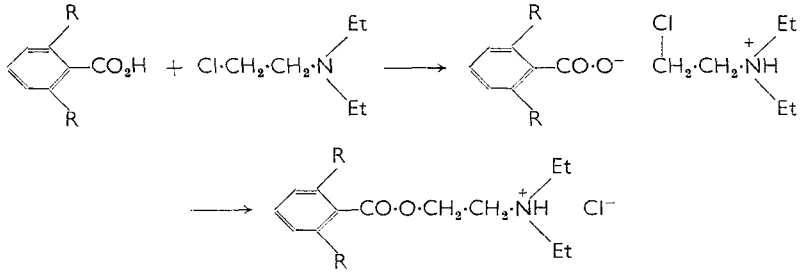


FIG. 2

The present method is based on the use of the carboxylate ion as a nucleophillic reagent in a normal aliphatic nucleophillic substitution reaction of a primary alkyl chloride. One possible problem of this method is the dimerisation of the chloroalkylamine. However, 2-diethyl-aminoethyl chloride is reasonably stable below 0° and as soon as the substituted benzoic acid is mixed with the base the proton from the acid is co-ordinated by the basic nitrogen atom to form the amino-conjugate acid, which is stable and cannot dimerise. The presence of a positive charge in the chloroalkylamine will favour a nucleophillic substitution of the chlorine atom by its inductive effect.

The reaction is of general application and is limited only by the tendency of any particular chloroalkylamine to self-condense. Probably the most reactive chloroalkylamine from this point of view is 2-dimethylaminoethyl chloride and even this may be used diluted with an equal volume of an inert solvent such as toluene and kept below 0° before mixing it with a substituted benzoic acid.

*Preparation of* 2,6-*Dimethylbenzoic Acid*

Three general methods of preparing this acid have been reported in the literature. Hufferd and Noyes (1921) prepared it from mesitylene by a method which was long and produced low yield. Fuson and others (1940) reported a better method of synthesis which involved the hydrolysis of the nitrile obtained from *m*-2-xylidine in a Sandmeyer reaction. However, the hydrolysis of 2,6-dimethylbenzonitrile proved difficult and a yield of 20 per cent was the best obtained. Häring (1960) recently modified the hydrolysis procedure and claimed a yield of 55 per cent.

Berger and Olivier (1927) converted 2,6-dimethylbenzonitrile to 2,6-dimethylbenzoic acid in a two-step procedure, going through 2,6-dimethylbenzamide as an intermediate, with an overall yield of 70 per cent for the hydrolysis. The method found most satisfactory in the present work for the hydrolysis of 2,6-dimethylbenzonitrile was that of Berger and Olivier (1927) but the overall yield of 2,6-dimethylbenzoic acid from *m*-2-xylidine was only 25 per cent.

Faber and Nauta (1951) have prepared 2,6-dimethylbenzoic acid from 2-bromo-*m*-xylene by carbonation of the corresponding Grignard reagent, and Jacobs and others (1951) carried out a similar reaction starting from 2-iodo-*m*-xylene. The latter authors claimed a yield of 73 per cent but they gave few experimental details. We have been unable to obtain a yield of this order using standard Grignard conditions. The main problem appeared to be the difficulty of forming a Grignard reagent. Grignard (1934) developed the "entrainment" method to overcome the difficulty. This involves adding an equimolar proportion of ethyl bromide, or some similarly active alkyl halide, to the reaction mixture. The effect of the ethyl bromide is a constant "cleaning" of the magnesium surface, thus permitting the reaction of acyl halide and magnesium to proceed at a satisfactory rate.

A comparison of the standard Grignard technique and the "entrainment" method for the preparation of benzoic acid and 2,6-dimethylbenzoic acid from bromobenzene and 2-iodo-*m*-xylene respectively has now been made. The quantities of organic reactants and the yield of products obtained are summarised in Table III. Using the "entrainment" method, 2,6-dimethylbenzoic acid was produced in very good yield.

TABLE III

A COMPARISON OF TWO METHODS OF THE GRIGNARD REACTION FOR THE PREPARATION OF BENZOIC ACID AND 2,6-DIMETHYLBENOZIC ACID

| Compound | Quantity of organic reactants | | By-products isolated | Yield of product | |
|---|---|---|---|---|---|
| | Bromobenzene | Ethyl bromide | | Wt. | Per cent |
| Benzoic acid | 26·5 g. $\frac{1}{6}$ mole<br>26·5 g. $\frac{1}{6}$ mole | Nil<br>18 g. $\frac{1}{6}$ mole | 2 g.<br>— | 13·2 g.<br>20·5 g. | 64<br>99·5 |
| | 2-Iodo-*m*-xylene | Ethyl bromide | *m*-Xylene | | |
| 2,6-Dimethylbenzoic acid | 38·7 g. $\frac{1}{6}$ mole<br>38·7 g. $\frac{1}{6}$ mole | Nil<br>18 g. $\frac{1}{6}$ mole | 1·7 g.<br>0·1 g. | 10·5 g.<br>22·7 g. | 42<br>90·7 |

*Preparation of 2,6-Difluorobenzoic Acid*

There are two general methods by which fluorine may be introduced into an aromatic ring using the Schiemann reaction. One is to diazotise the amino-group by the usual method and then form the diazonium fluoroborate by adding the fluoroborate ion. The second method is to carry out the diazotisation reaction in the presence of the fluoroborate ion. Both these methods have now been examined for the preparation of 2,6-difluorobenzoic acid and it was found that the second method was preferable because less phenolic by-products were formed; the reaction could be carried out at 0–5° and hence the reaction time was shorter; the

yield of aromatic fluoro-compound was higher and more consistent when the diazonium fluoroborate prepared by the second method was decomposed.

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## REFERENCES

Berger, G. and Olivier, S. C. J. (1927). *Rec. Trav. Chim.*, **46**, 600–604.
Brady, O. L. and Taylor, A. (1920). *J. chem. Soc.*, **117**, 876–880.
Childress, S. J., Cordasco, M. G., Plekss, O. J. and Reiner, L. (1954). *J. Amer. chem. Soc.*, **76**, 3988–3991.
Dvoretzky, J. and Richter, G. H. (1953). *J. org. Chem.*, **18**, 615–619.
Faber, A. C. and Nauta N. Th. (1951). *Rec. Trav. Chim.*, **70**, 659–662.
Foldes, F. F. and Rhodes, D. H. (1953). *Current Researches in Anaesthesia and Analgesics*, **32**, 305–318.
Grignard, V. (1934). *C.R. Acad. Sci., Paris*, **198**, 625–628.
Fuson, R. C., Scott, S. C., Horning, E. C. and McKeever, C. H. (1940). *J. Amer. chem. Soc.*, **62**, 2091–2094.
Häring, M. (1960). *Helv. Chim. Acta.*, **43**, 104–113.
Hufferd, R. W. and Noyes, W. A. (1921). *J. Amer. chem. Soc.*, **43**, 925–935.
Jacobs, T. L., Reed, R. and Pacovska, E. (1951). *Ibid.*, **73**, 4505–4509.
Lock, G. (1936). *Ber.*, **69**, 2253–2258.
Norris, J. F. and Bease, A. E. (1940). *J. Amer. chem. Soc.*, **62**, 953–956.
Rabjohn, N., Fronabarger, J. W. and Linstromberg, W. W. (1955). *J. Org. Chem.*, **20**, 271–273.
Robinson, M. M. and Robinson, B. L. (1956). *Organic Syntheses*, **36**, 94.
Sirks, H. A. (1908). *Rec. Trav. Chim.*, **27**, 217–222.
Slotta, K. H. and Benisch, R. (1935). *Ber.*, **68**, 754–761.
Stoker, J. R. (1960). *M.Sc. Thesis, Manchester University.*
Thomas, J. and Buckley, D. (1962). *J. Pharm. Pharmacol.*, **14**, 225–231.
Thomas, J. and Stoker, J. R. (1961). *Ibid.*, **13**, 129–138.