Bromination of 3-Amino- and 3-Dimethylamino-pyridine

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3-Dimethylaminopyridine and 2,4,4,6-tetrabromocyclohexa-2,5-dienone react to give exclusively 2-bromo-5-dimethylaminopyridine, but 3-aminopyridine gives a mixture of 3-amino-2-bromo- and 3-amino-2,6-dibromo-pyridine. 2-Amino- and 2-dimethylamino-pyridine and 2-aminopyrimidine are attacked at the 5-position. Convenient syntheses of 3-dimethylaminopyridine and 2-amino-5-dimethylaminopyridine are described.

As part of a general study of steric and electronic effects in di- and tri-arylmethane dyes,[1] the key intermediate 2-bromo-5-dimethylaminopyridine had to be prepared. Previous work on the halogenation of 3-aminopyridine has illustrated that attack is directed predominantly to the 2-position,[2-5] and consequently the introduction of a bromine atom *para* to the 3-dimethylamino-group by indirect methods has been studied.

Dimethylation of the amino-group in 5-amino-2-bromopyridine, prepared from 2-amino-5-nitropyridine,[6] could not be accomplished with methyl iodide, dimethyl sulphate, or formaldehyde–formic acid,[7] although the last reagent is successful with both 3-aminopyridine and the isomeric 2-amino-5-bromopyridine.

2-Amino-5-dimethylaminopyridine (I) was synthesised from 2-amino-5-bromopyridine *via* 5-bromo-2-nitropyridine[8] and 5-dimethylamino-2-nitropyridine. Selective replacement of the 2-amino-group in compound (I) could not be achieved, although many bromopyridines have been prepared from the corresponding 2- or 4-amino-compounds, especially by use of the technique developed by Craig.[9] Diazotisation of the perbromide of compound (I) under the conditions previously described[6] gave four products, none being the desired bromopyridine. Electrophilic attack at C-3 and C-6 and replacement of the amino-substituent by a hydroxy-group could account for the formation of several products.

2,4,4,6-Tetrabromocyclohexa-2,5-dienone is known to be a selective *para*-brominating agent for a variety of phenols[10] and amines.[11] Reaction with 3-dimethylaminopyridine in dichloromethane at 0° gave 2-bromo-5-dimethylaminopyridine free from 2-bromo-3-dimethylaminopyridine and dibromo-compounds. The synthesis of 3-dimethylaminopyridine from the primary amine by reaction with formaldehyde and formic acid[7] was more reliable and convenient than the route described by

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Binz and Schickh [12] and was easily adapted to large-scale work.

The dienone reacts with 3-aminopyridine under the same conditions to yield a mixture of products, from which 3-amino-2-bromopyridine, 3-amino-2,6-dibromopyridine, and 3-aminopyridine were separated by column chromatography. The formation of the dibromo-compound under these mild conditions further illustrates the ease with which 3-aminopyridine undergoes bromination.

The differing behaviour of 3-amino- and 3-dimethylamino-pyridine towards the dienone reagent may largely be a result of steric factors. The crowding effect of a dimethylamino-group is considerably greater than that of the amino-group,[13] so that approach of the attacking reagent to the 2-position will be more difficult in 3-dimethylaminopyridine than in the primary amine.

In an extension of the use of the dienone, we have found that 2-aminopyridine affords 2-amino-5-bromopyridine (75%) free from the 3,5-dibromo-compound. By conventional bromination techniques, 2-aminopyridine affords both 5-bromo- and 3,5-dibromo-2-aminopyridine.[14] 2-Dimethylaminopyridine also gives the 5-bromo-derivative (70%), as does 2-aminopyrimidine (82%).[15]

EXPERIMENTAL

^{1}H N.m.r. spectra (100 MHz) were obtained with a Varian HA 100 spectrometer for solutions in deuteriochloroform at the Physico-Chemical Measurement Unit, Harwell.

5-Bromo-2-nitropyridine.— 2-Amino-5-bromopyridine (13·8 g) dissolved in concentrated sulphuric acid (50 ml) was added dropwise to a mixture of hydrogen peroxide (100 ml; 30%) and concentrated sulphuric acid (200 ml) cooled in ice–water. After 48 h at room temperature, the mixture was poured into a large excess of ice–water. Crystallisation of the precipitated solid from methanol gave the nitro-compound (78%), m.p. 148—150° (lit.,[8] 149—150°).

5-Dimethylamino-2-nitropyridine.—A mixture of 5-bromo-2-nitropyridine (2 g), ethanol (5 ml), and ethanolic dimethylamine (5 ml; 33%) was heated in a sealed tube at 80° for 66 h. The solid which precipitated when the contents of the tube were poured into water was crystallised from ethanol to give yellow needles of *5-dimethylamino-2-nitropyridine* (45%), m.p. 201—203° (Found: C, 50·2; H, 5·3; N, 24·9. $C_7H_9N_3O_2$ requires C, 50·3; H, 5·4; N, 25·2%), τ 1·86 (1H, d, $J_{3,4}$ 9·0 Hz, 3-H), 2·06 (1H, d, $J_{4,6}$ 3·0 Hz, 6-H), 3·02 (1H, dd, $J_{3,4}$ 9·0, $J_{4,6}$ 3·0 Hz, 4-H), and 6·85 (6H, s, NMe_2).

2-Amino-5-dimethylaminopyridine.— 5-Dimethylamino-2-nitropyridine (5 g) in ethanol (20 ml) was added to a suspension of tin(II) chloride (25 g) in ethanol (25 ml). After a short time, a vigorous reaction occurred and the mixture was subsequently heated on a steam-bath for 30 min. The solvent was removed under reduced pressure and the residue was neutralised initially with ethanolic potassium hydroxide and finally with sodium carbonate; the amine was extracted continuously with chloroform. Removal of the solvent from the dried (Na_2SO_4) extracts gave a residue which was distilled to give *2-amino-5-dimethylaminopyridine* (63%), b.p. 158—160° at 12 mmHg, m.p. 48—50° (Found: C, 61·6; H, 7·5; N, 30·9. $C_7H_{11}N_3$ requires C, 61·3; H, 7·8; N, 30·7%), τ 2·33 (1H, d, $J_{4,6}$ 3·0 Hz, 6-H), 2·97 (1H, dd, $J_{3,4}$ 9·0, $J_{4,6}$ 3·0 Hz, 4-H), 3·55 (1H, d, $J_{3,4}$ 9·0 Hz, 3-H), 6·04 (2H, s, NH_2), and 7·20 (6H, s, NMe_2). The *acetyl derivative* had m.p. 163—165° (from ethanol) (Found: C, 60·4; H, 7·3; N, 23·8. $C_9H_{13}N_3O$ requires C, 60·3; H, 7·3; N, 23·5%).

3-Dimethylaminopyridine.—A mixture of 3-aminopyridine (9·3 g), formic acid (26 ml; 98%), and aqueous formaldehyde (22 ml; 40%) was heated at 100° for 19 h. The cooled solution was acidified with dilute hydrochloric acid and was evaporated to dryness under reduced pressure. Basification, extraction of the liberated base with chloroform, removal of the solvent from the dried (Na_2SO_4) extracts, and distillation of the residue afforded 3-dimethylaminopyridine (68%), b.p. 125—127° at 30 mmHg (lit.,[12] 108—110° at 12 mmHg).

2-Bromo-5-dimethylaminopyridine.—A suspension of 2,4,4,6-tetrabromocyclohexa-2,5-dienone (20·5 g) in dichloromethane (100 ml) was added during 30 min to a solution of 3-dimethylaminopyridine (6·1 g) in dichloromethane (50 ml) maintained at −10°. The mixture was warmed to room temperature during 30 min and was then extracted with 2M-sodium hydroxide solution (2 × 25 ml). The organic layer was washed with water and dried ($MgSO_4$). Removal of the solvent and distillation of the residue yielded *2-bromo-5-dimethylaminopyridine* (60%), b.p. 164—166° at 20 mmHg, m.p. 70·5—71° [from light petroleum (b.p. 60—80°)] (Found: C, 41·9; H, 4·5; Br, 39·5; N, 13·9. $C_7H_9BrN_2$ requires C, 41·8; H, 4·5; Br, 39·8; N, 13·9%), τ 2·18 (1H, d, $J_{4,6}$ 3·5 Hz, 6-H), 2·77 (1H, d, $J_{3,4}$ 9·0 Hz, 3-H), 3·15 (1H, dd, $J_{3,4}$ 9·0, $J_{4,6}$ 3·5 Hz, 4-H), and 7·06 (6H, s, NMe_2).

Reaction between 3-Aminopyridine and 2,4,4,6-Tetrabromocyclohexa-2,5-dienone.—3-Aminopyridine (3·76 g) and the dienone (16·4 g) reacted as described in the foregoing experiment to give a solid (4·2 g). Elution from neutral alumina with benzene–chloroform (9 : 1) gave 3-amino-2,6-dibromopyridine (14%), m.p. 141—142° (lit.,[3] 142°) [from light petroleum (b.p. 80—100°)], τ 2·80 (1H, d, $J_{4,5}$ 8·5 Hz, 5-H), 3·11 (1H, d, $J_{4,5}$ 8·5 Hz, 4-H), and 6·24br (2H, s, NH_2). Further elution gave 3-amino-2-bromopyridine (67%), m.p. 78—79° (lit.,[16] 79°) [from light petroleum (b.p. 60—80°)], τ 2·24 (1H, m, 6-H), 2·98 (2H, m, 4- and 5-H), and 6·23br (2H, s, NH_2). Finally, elution with chloroform afforded unchanged 3-aminopyridine (14%).

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