# Sodium Borohydride Reduction of Adducts of Primary Amines with Aldehydes and *p*-Thiocresol. The Alkylation of Heterocyclic and Aromatic Amino-compounds

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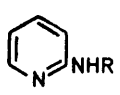
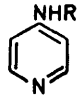
*p*-Nitroaniline, 2-aminopyridine (1a), 4-aminopyridine (2a), 2-amino-4-methylpyrimidine (8a), 2-aminothiazole (10a), and 2-aminobenzimidazole (12a) react with aqueous formaldehyde and *p*-thiocresol in ethanol or methanol solution to give *N*-(*p*-tolylthiomethyl) derivatives [corresponding to the general formula (4; $R^2$ = H)], usually in high yields. When the latter compounds are heated, under reflux, with an excess of sodium borohydride in ethanol or 1,2-dimethoxyethane solution, the corresponding methylamino-compounds [general formula (5; $R^2$ = H)] are obtained. By a similar two-step procedure in which aqueous formaldehyde is replaced, as appropriate, by anhydrous acetaldehyde, propionaldehyde, or benzaldehyde, *p*-nitroaniline is converted into *N*-ethyl-*p*-nitroaniline, *p*-chloroaniline is converted into *p*-chloro-*N*-(n-propyl)aniline, (1a) is converted into the corresonding ethylamino- and benzylamino-compounds (1c) and (1d), respectively, and (10a) and (12a) are converted into their 2-*N*-(n-propyl) derivatives (10c) and (12c), respectively.

THE widespread natural occurrence, especially in transfer ribonucleic acids (tRNA), of modified ribonucleosides [1] in which amino- are replaced by methylamino- or dimethylamino-substituents encouraged us to search for a procedure [2,3] suitable for the alkylation of the common ribonucleosides (*i.e.* adenosine, cytidine, and guanosine) on their exocyclic amino-groups. It is well established that 'amidine-like' heterocyclic amino-compounds, such as 2-aminopyridine (1a), react [4] with alkylating agents of the type R–X on their endocyclic nitrogen atoms and the same is true for vinylogous systems [*e.g.* 4-aminopyridine (2a)]. As far as we are aware, no general method for the alkylation of such heterocyclic

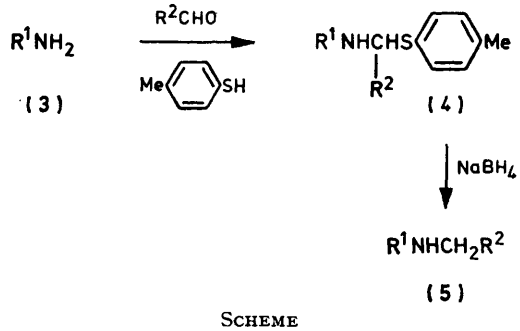


(1)
a; R = H
b; R = Me
c; R = Et
d; R = $PhCH_2$



(2)
a; R = H
b; R = Me

amino-compounds on their exocyclic nitrogen atoms has so far been reported in the literature. We have therefore examined the suitability of our nucleoside alkylation procedure [2,3] for this purpose and now report some alkylation studies involving simple aromatic and heterocyclic substrates.



SCHEME

Our alkylation procedure is indicated in outline in the Scheme. A primary amino-compound (3) is allowed to react with an aldehyde and *p*-thiocresol to give the intermediate *N*-[1-(*p*-tolylthio)alkyl]-derivative (4) which is then treated with sodium borohydride to give the desired product (5). Long before we began our original studies with ribonucleosides and their derivatives, Grillot and Schaffrath had shown [5] that primary aromatic amines (3; $R^1$ = aryl) reacted with formaldehyde and thiophenols to give *N*-arylthiomethyl derivatives (corresponding to 4; $R^1$ = aryl, $R^2$ = H). We first confirmed this general observation by heating a solution of *p*-nitroaniline, aqueous formaldehyde (1.6 mol equiv.) and *p*-thiocresol (2.0 mol equiv.) in ethanol (Table 1, experiment no. 1), under reflux, for 2.5 h and isolating *p*-nitro-*N*-(*p*-tolylthiomethyl)aniline (4; $R^1$ = 4-$O_2NC_6H_4$, $R^2$ = H) from the products in 94% yield. We then showed that this reaction could also be carried out with aldehydes other than formaldehyde. Thus satisfactory yields of adducts [(4; $R^1$ = 4-$O_2NC_6H_4$, $R^2$ = Me) and (4; $R^1$ = 4-$ClC_6H_4$, $R^2$ = Et), respectively] were obtained in the reactions between (i) *p*-nitroaniline, acetaldehyde, and *p*-thiocresol (Table 1, experiment no. 2) and (ii) *p*-chloroaniline, propionaldehyde, and *p*-thiocresol (Table 1, experiment no. 3; see also Table 2, experiment no. 3).

When *p*-nitro-*N*-(*p*-tolylthiomethyl)aniline (4; $R^1$ = 4-$O_2NC_6H_4$, $R^2$ = H) was heated with sodium borohydride (1.3 mol equiv.), under reflux, in 1,2-dimethoxyethane (glyme) solution for 15 min (Table 2, experiment no. 1), *N*-methyl-*p*-nitroaniline (5; $R^1$ = 4-$O_2NC_6H_4$, $R^2$ = H) was obtained and isolated from the products as a crystalline solid in 84% yield. The other two adducts derived from aromatic amines (4; $R^1$ = 4-$O_2NC_6H_4$, $R^2$ = Me) and (4; $R^1$ = 4-$ClC_6H_4$, $R^2$ = Et) were similarly reduced by treatment with sodium borohydride to give (Table 2, experiments nos. 2 and 3) the corresponding *para*-substituted *N*-alkylanilines (5; $R^1$ = 4-$O_2NC_6H_4$, $R^2$ = Me and 5; $R^1$ = 4-$ClC_6H_4$, $R^2$ = Et) in satisfactory yields.

We then turned our attention towards the alkylation

TABLE 1

Reactions between primary amino-compounds, aldehydes, and *p*-thiocresol

| Expt. no. | Substrate | Aldehyde | Solvent [a] | *t*/h | Isolated yield (%) | M.p. (°C) |
|---|---|---|---|---|---|---|
| 1 | *p*-nitroaniline | $CH_2O$ | A | 2.5 | 94 | 123—124 |
| 2 | *p*-nitroaniline | MeCHO | A | 3 | 97 | 55—56 |
| 3 | *p*-chloroaniline | EtCHO | A | 8 | *b* | |
| 4 | (1a) | $CH_2O$ | B | 1.75 | 75 | 68 |
| 5 | (1a) | MeCHO | B | 2 | *b* | |
| 6 | (1a) [c] | PhCHO | A | 2 | 88 | 61—62 |
| 7 | (2a) [d] | $CH_2O$ | A | 3 | *b* | |
| 8 | (8a) [e] | $CH_2O$ | A | 6 | 61 | |
| 9 | (10a) | $CH_2O$ | A | 2 | 80 | 52—54 |
| 10 | (10a) | EtCHO | A | 2 | *b* | |
| 11 | (12a) | $CH_2O$ | A | 7 | 87 | 156—158 |
| 12 | (12a) | EtCHO | A | 3 | 80 | |

[a] The reaction mixtures were heated, under reflux, in ethanol (A) or methanol (B). [b] The adducts were not isolated pure and the crude products were reduced directly with sodium borohydride (Table 2). [c] 2-Aminopyridine was heated with benzaldehyde in ethanol, under reflux, for 0.5 h before *p*-thiocresol was added. The reaction was then allowed to proceed for a further 1.5 h. [d] Acetic acid (0.55 mol equiv. with respect to substrate) was added to the reaction medium. [e] Acetic acid (0.2 mol equiv. with respect to substrate) was added to the reaction medium.

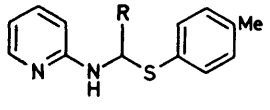
TABLE 2

Sodium borohydride reduction of *N*-*p*-tolylthioalkyl derivatives

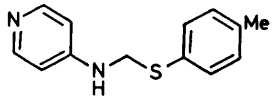
| Expt. no. | Solvent [a] | *t* [b]/h | Isolated product | Yield (%) | M.p. (°C) |
|---|---|---|---|---|---|
| 1 | B | 0.5 | *N*-methyl-*p*-nitroaniline | 84 | 150 |
| 2 | B | 0.5 | *N*-ethyl-*p*-nitroaniline | 86 | 96 |
| 3 | B | 2 | *p*-chloro-*N*-(propyl)aniline | 50 [c] | *d* |
| 4 | B | 2 | (1b) | 87 | 188—190 [e] |
| 5 | B | 2.5 | (1c) | 82 [c] | 140—142 [e] |
| 6 | B | 1.0 | (1d) [f] | 75 | 148—150 [e] |
| 7 | A | 1.0 | (2b) | 58 [c] | 117—118 |
| 8 | A | 1.25 | (8b) | 89 | 54—55 |
| 9 | B | 0.75 | (10b) | 95 | 190 (decomp) [e] |
| 10 | B | 1.7 | (10c) | 81 [c] | 153—154 [e] |
| 11 | A | 0.75 | (12b) | 76 | 167—168 |
| 12 | A | 1.9 | (12c) | 65 | 140 |

[a] The reaction mixtures were heated, under reflux, in ethanol (A) or 1,2-dimethoxyethane (B). [b] This includes the time taken to add the sodium borohydride to the solution of substrate. [c] Overall yield, based on amino-compound. [d] Isolated as oil and not converted into picrate. [e] M.p. of picrate. [f] Isolated only as picrate.

of heterocyclic amino-compounds. We had earlier shown [2] that 2-aminopyridine (1a) reacted with formaldehyde and *p*-thiocresol in boiling methanol solution to give the expected adduct (6a) in 65% isolated yield. We now report that when the latter compound (6a),



(6) a; R = H
b; R = Me
c; R = Ph

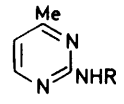


(7)

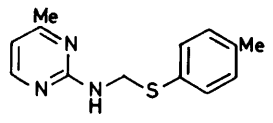
which was obtained in an improved yield (Table 1, experiment no. 4), was heated with sodium borohydride, under reflux, in glyme solution, 2-methylaminopyridine (1b) was obtained in high yield (Table 2, experiment no. 4) and characterized as its crystalline picrate. In the same way, 2-aminopyridine (1a) was allowed to react with acetaldehyde and *p*-thiocresol in boiling methanol solution (Table 1, experiment no. 5) and the resulting crude adduct (6b) was reduced directly with sodium borohydride in glyme solution (Table 2, experiment no. 5) to give 2-ethylaminopyridine (1c) in 82% overall yield. 2-Aminopyridine (1a) was converted into 2-[α-(*p*-tolylthio)benzylamino]pyridine (6c) by allowing it to react first with benzaldehyde in boiling ethanol solution and then adding *p*-thiocresol (Table 1, experiment no. 6). When the latter adduct (6c), which was isolated as a crystalline solid, was heated with sodium borohydride in glyme solution (Table 2, experiment no. 6), 2-benzylaminopyridine (1d) was obtained and isolated from the products in 75% yield. The conversion (Table 1, experiment no. 7) of 4-aminopyridine (2a) into 4-(*p*-tolylthiomethylamino)pyridine (7) proceeded more rapidly when a small quantity of acetic acid [0.55 mol equiv. with respect to (2a)] was added to the reaction mixture. Reduction of the crude adduct (7) with sodium borohydride in boiling ethanol solution (Table 2, experiment no. 7) gave 4-methylaminopyridine (2b) which was isolated as a crystalline solid in 58% overall yield.

The alkylation of three other heterocyclic amino-compounds was investigated. First, 2-amino-4-methylpyrimidine (8a) was converted, again in the presence of a small quantity of acetic acid (Table 1, experiment no. 8) into 4-methyl-2-(*p*-tolylthiomethylamino)pyrimidine (9) which was then reduced with sodium borohydride (Table 2, experiment no. 8) to give 4-methyl-2-methyl-

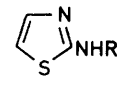
aminopyrimidine (8b) as a crystalline solid in high yield. Secondly, 2-aminothiazole (10a) was converted into both 2-methylamino- and 2-(n-propylamino)-thiazoles [(10b) and (10c), respectively]; (10a) reacted with formaldehyde and *p*-thiocresol in boiling ethanol solution (Table 1, experiment no. 9) to give the intermediate *p*-tolylthiomethyl derivative (11a) which was isolated as a crystalline solid and then reduced with sodium borohydride



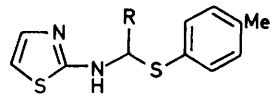
(8) a; R = H
b; R = Me



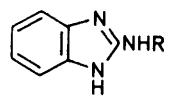
(9)



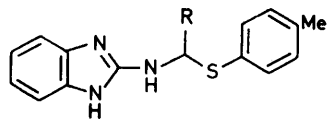
(10) a; R = H
b; R = Me
c; R = $MeCH_2CH_2$



(11) a; R = H
b; R = Et



(12) a; R = H
b; R = Me
c; R = $MeCH_2CH_2$



(13) a; R = H
b; R = Et

(Table 2, experiment no. 9) to give (10b) in high yield. When 2-aminothiazole (10a) was treated with propionaldehyde and *p*-thiocresol (Table 1, experiment no. 10) and the crude product (11b) reduced directly with sodium borohydride (Table 2, experiment no. 10), 2-(n-propylamino)thiazole (10c) was obtained and isolated in satisfactory overall yield. Finally, 2-aminobenzimidazole (12a) was similarly converted into the corresponding methylamino- and n-propylamino-derivatives [(12b) and (12c), respectively] (Table 1, experiment nos. 11 and 12 and Table 2, experiment nos. 11 and 12). Both the latter compounds were obtained as crystalline solids in good isolated yields.

Although the alkylation of only five different heterocyclic amino-compounds has been undertaken in this study, the range of the examples described here and in the previous studies [2,3] involving ribonucleoside derivatives is such that it seems reasonable to conclude that the alkylation procedure is likely to be of general application. Furthermore, it should be noted that four different aldehydes have been used and four different alkyl groups have thereby been introduced. The present alkylation procedure is related to methods involving [6] the reduction of Schiff's bases and to a number of methylation procedures involving formaldehyde. Especially notable among the latter are Eschweiler–Clarke methylation [7] with formaldehyde and formic acid, Borsch and Hassid's method [8] involving formaldehyde and sodium cyanoborohydride, and Kadin's method [9] involving the sodium borohydride reduction of *N*-succinimidomethylene derivatives of amino-compounds. Our studies suggest that the present procedure is more selective than the first two [7,8] methods and of wider application than the third.[9]

## EXPERIMENTAL

Unless otherwise stated, $^1H$ and $^{13}C$ n.m.r. spectra were measured with Bruker WH 250 and HFX 90 FT spectrometers, respectively. Mass spectra were obtained with A.E.I. MS 902 and VG ZAB-1F spectrometers. U.v. absorption spectra were measured with a Perkin-Elmer model 403 or a Cary model 17 spectrophotometer. T.l.c. and short-column chromatography were carried out on Merck silica gel 60 $F_{254}$ plates and Merck silica gel H, respectively.

N-*Methyl*-p-*nitroaniline*.—A solution of *p*-nitroaniline (3.3 g, 23.9 mmol), aqueous formaldehyde (*ca.* 39% w/v; 3.0 ml, 39 mmol), and *p*-thiocresol (5.95 g, 48 mmol) in ethanol (120 ml) was heated, under reflux, for 2.5 h. The cooled products deposited p-*nitro*-N-(p-*tolylthiomethyl*)-*aniline* (Found: C, 61.3; H, 5.2; N, 10.0. $C_{14}H_{14}N_2O_2S$ requires C, 61.3; H, 5.1; N, 10.2%) as yellow prisms, m.p. 123—124 °C (6.16 g, 94%); $M^+$, 274 (75%).

Sodium borohydride (0.185 g, 5.0 mmol) was added over 15 min to a solution of the above product (1.05 g, 3.8 mmol) in 1,2-dimethoxyethane (7 ml). The reaction mixture was then heated on a steam-bath for 15 min, cooled, and treated with methanol (10 ml). After the products had been neutralized with acetic acid and concentrated under reduced pressure, acetone (50 ml) was added and the resulting suspension was filtered. The filtrate was concentrated under reduced pressure and the residue obtained was triturated with light petroleum (b.p. 60—80 °C) and then crystallized from ethanol to give *N*-methyl-*p*-nitroaniline (Found: C, 55.2; H, 5.4; N, 18.3. Calc. for $C_7H_8N_2O_2$: C, 55.25; H, 5.3; N, 18.4%), m.p. 150 °C (lit.,[10] 148.5—149.5 °C) (0.49 g, 84%); $M^+$, 152 (100%); δ [$(CD_3)_2CO$–$D_2O$] 2.91 (3 H, s), 6.68 (2 H, m), and 8.05 (2 H, m).

N-*Ethyl*-p-*nitroaniline*.—A solution of *p*-nitroaniline (3.3 g, 23.9 mmol), acetaldehyde (2.7 ml, 47.8 mmol), and *p*-thiocresol (6.2 g, 50 mmol) in ethanol (170 ml) was heated, under reflux, for 3 h to give (*p*-nitro-*N*-[1-(*p*-tolylthio)ethyl]-aniline [Found (in material recrystallized from ethanol): C, 62.5; H, 5.7; N, 9.7. $C_{15}H_{16}N_2O_2S$ requires C, 62.5; H, 5.6; N, 9.7%], m.p. 55—56 °C (6.69 g, 97%).

The latter compound (1.15 g, 4.0 mmol) was reduced with sodium borohydride (0.148 g, 4.0 mmol) in 1,2-dimethoxyethane (7 ml) and worked-up according to the procedure described for the preparation of *p*-nitro-*N*-methylaniline. The required *p*-nitro-*N*-ethylaniline (Found: C, 57.9; H, 6.15; N, 16.7. $C_8H_{10}N_2O_2$ requires C, 57.8; H, 6.1; N, 16.85%) had m.p. 96 °C (lit.,[11] 96 °C) (0.569 g, 86%); $M^+$, 166 (6%); $\delta_H$ [$(CD_3)_2CO$–$D_2O$] 1.26 (3 H, t, *J* 7.3 Hz), 3.28 (2 H, q, *J* 7.3 Hz), 6.69 (2 H, m), 8.03 (2 H, m); $\delta_C$ [$(CD_3)_2CO$] 14.32 and 38.30.

p-*Chloro*-N-(*n-propyl*)*aniline*.—A solution of *p*-chloroaniline (2.4 g, 18.8 mmol), *p*-thiocresol (2.98 g, 24.0 mmol), and propionaldehyde (1.6 ml, 22.2 mmol) in ethanol (60 ml) was heated, under reflux, for 8 h. The products were then concentrated under reduced pressure and the oily residue

was dissolved in 1,2-dimethoxyethane (30 ml). Sodium borohydride (1.24 g, 33.5 mmol) was added to the latter solution over a period of 10 min and the reactants were then heated under reflux. After 1.5 h, the products were cooled to room temperature, treated with methanol (20 ml) and 1M-hydrochloric acid (40 ml), and concentrated under reduced pressure. The residue obtained was partitioned between 1M-hydrochloric acid (40 ml) and diethyl ether (30 ml). The ether layer was rejected and the aqueous layer was further washed with diethyl ether (2 × 30 ml) before it was neutralized (to *ca.* pH 7—8) with 2M-aqueous sodium hydroxide and extracted with dichloromethane (3 × 30 ml). The dried ($MgSO_4$), combined, dichloromethane extracts were carefully evaporated under reduced pressure to give *p*-chloro-*N*-(n-propyl)aniline (1.6 g, 50%) (Found: $M^+$, 169.0659. Calc. for $C_9H_{12}{}^{35}ClN$: *M*, 169.0659); $\delta_H$ [$(CD_3)_2SO$–$D_2O$] 0.93 (3 H, t, *J* 7.6 Hz), 1.55 (2 H, m), 2.9 (2 H, t, *J* 7.1 Hz), 6.56 (2 H, m), and 7.08 (2 H, m); $\delta_C$ ($CDCl_3$) 11.50, 22.53, and 45.80.

2-*Methylaminopyridine* (1b).—A solution of 2-aminopyridine (1.9 g, 20.2 mmol), aqueous formaldehyde (*ca.* 39% w/v; 1.6 ml, 20.8 mmol) and *p*-thiocresol (2.5 g, 20.1 mmol) in methanol (100 ml) was heated, under reflux, for 105 min. The solvent was removed by evaporation and the residue was crystallised from cyclohexane to give 2-(*p*-tolylthiomethylamino)pyridine, m.p. 68 °C (lit.,[2] 68 °C) (3.5 g, 75%).

Sodium borohydride (0.074 g, 2.0 mmol) was added over 15 min to a solution of the above product (0.44 g, 1.9 mmol) in 1,2-dimethoxyethane (5 ml). After the reaction mixture had been heated, under reflux, on a steam-bath for 105 min, the products were worked-up according to the procedure described above in the preparation of *p*-chloro-*N*-(n-propyl)-aniline to give 2-methylaminopyridine (0.181 g, 87%).

A saturated alcoholic solution of picric acid (2 ml) was added to a solution of the above sample of 2-methylaminopyridine (0.10 g, 0.92 mmol) in ethanol (2 ml). The resulting mixture was heated on a steam-bath for 5 min, cooled, and filtered. Recrystallization of the residue from ethanol gave *2-methylaminopyridine picrate* [Found (in material dried *in vacuo* at 90 °C): C, 42.5; H, 3.4; N, 20.7. $C_{12}H_{11}N_5O_7$ requires C, 42.7; H, 3.3; N, 20.8%], (0.293 g, 94%), m.p. 188—190 °C (lit.,[12] 193—194 °C); $\delta_H$ [$(CD_3)_2SO$, 90 MHz] 3.00 (3 H, s), 6.7—7.1 (2 H, m), 7.75—8.0 (2 H, m), and 8.63 (2 H, s).

2-*Ethylaminopyridine* (1c).—A solution of 2-aminopyridine (2.8 g, 29.8 mmol), acetaldehyde (2.8 ml, 49.6 mmol), and *p*-thiocresol (5.0 g, 40.3 mmol) in methanol (80 ml) was heated, under reflux, for 2 h. The products were then concentrated under reduced pressure and the residue was dissolved in 1,2-dimethoxyethane (80 ml). Sodium borohydride (2.748 g, 74.3 mmol) was added to the latter solution over 15 min and the reactants were then heated under reflux. After 2.5 h, the products were worked-up according to the procedure described above in the preparation of *p*-chloro-*N*-(n-propyl)aniline to give 2-ethylaminopyridine (2.97 g, 82%).

A saturated alcoholic solution of picric acid (8 ml) was added to a solution of the above sample of 2-ethylaminopyridine (0.50 g, 4.1 mmol) in ethanol (5 ml). Recrystallization of the product from aqueous ethanol gave *2-ethylaminopyridine picrate* [Found (in material dried *in vacuo* at 60 °C): C, 44.3; H, 4.0; N, 20.0. $C_{13}H_{13}N_5O_7$ requires C, 44.45; H, 3.7; N, 19.9%], (1.294 g, 90%), m.p. 140—142 °C; $\delta_H$ [$(CD_3)_2SO$–$CD_3OD$, 90 MHz] 1.29 (3 H, t, *J* 7.2 Hz), 3.38 (2 H, q, *J* 7.2 Hz), 6.8—7.1 (2 H, m), 7.75—8.0 (2 H, m), and 8.66 (2 H, s).

2-*Benzylaminopyridine* (1d).—A solution of 2-aminopyridine (2.0 g, 21.3 mmol) and benzaldehyde (3.5 ml, 34.5 mmol) in ethanol (35 ml) was heated, under reflux, for 30 min. *p*-Thiocresol (7.0 g, 56.4 mmol) was then added and the reaction solution was heated for a further 90 min. The products were then concentrated under reduced pressure and recrystallized from light petroleum (b.p. 60—80 °C) to give 2-[α-(*p*-tolylthio)benzylamino]pyridine (6c) as yellow crystals, m.p. 61—62 °C (5.74 g, 88%).

Sodium borohydride (0.111 g, 3.0 mmol) was added over a period of 10 min to a solution of the above product (1.2 g, 3.9 mmol) in 1,2-dimethoxyethane (3 ml). After the reaction mixture had been heated, under reflux, on a steam-bath for 1 h, the products were worked up according to the procedure described above in the preparation of *p*-chloro-*N*-(n-propyl)aniline. A solution of the oily product obtained in ethanol (5 ml) was treated with saturated alcoholic picric acid (6 ml). Recrystallization of the product from ethanol gave *2-benzylaminopyridine picrate* [Found (in material dried *in vacuo* at 60 °C): C, 52.4; H, 3.75; N, 16.9. $C_{18}H_{15}N_5O_7$ requires C, 52.3; H, 3.65; N, 16.9%], {1.22 g, 75% based on 2-[α-(*p*-tolylthio)benzylamino]pyridine}, m.p. 148—150 °C; $\delta_H$ [$(CD_3)_2SO$–$D_2O$; 90 MHz] 4.52 (2 H, s), 6.75—7.1 (2 H, m), 7.33br (5 H, s), 7.7—8.0 (2 H, m), and 8.55 (2 H, s).

4-*Methylaminopyridine* (2b).—A solution of 4-aminopyridine (1.504 g, 16.0 mmol), aqueous formaldehyde (*ca.* 39% w/v; 2.46 ml, 32.0 mmol), *p*-thiocresol (3.97 g, 32.0 mmol), and acetic acid (0.5 ml, 8.7 mmol) in ethanol (20 ml) was heated, under reflux, for 3 h and the cooled products were then concentrated under reduced pressure. Sodium borohydride (1.10 g, 30 mmol) was added over a period of 10 min to a solution of the residue obtained in ethanol (30 ml). The reactants were then heated, under reflux, for 1 h and the products were worked-up as described above in the preparation of *p*-chloro-*N*-(n-propyl)aniline except that ethyl acetate was used in the final extractions. Crystallization of the product from benzene gave 4-methylaminopyridine (Found: C, 66.4; H, 7.5; N, 26.0. Calc. for $C_6H_8N_2$: C, 66.6; H, 7.4; N, 25.9%) (1.01 g, 58% based on 4-aminopyridine), m.p. 117—118 °C (lit.,[13] 124.5—125 °C); $M^+$, 108 (100%); $\delta_H$ [$(CD_3)_2SO$–$D_2O$] 2.70 (3 H, s), 6.47 (2 H, m), and 8.00 (2 H, m); $\delta_C$ [$(CD_3)_2SO$] 28.48, 106.82, 149.33, and 154.37; $\lambda_{max.}$ (95% EtOH) 253 (ε 18 000), $\lambda_{min.}$ 231 nm (ε 2 500).

4-*Methyl*-2-*methylaminopyrimidine* (8b).—A solution of 2-amino-4-methylpyrimidine (1.81 g, 16.6 mmol), aqueous formaldehyde (*ca.* 39% w/v; 1.9 ml, 24.7 mmol), *p*-thiocresol (3.098 g, 24.9 mmol), and acetic acid (0.2 ml, 3.5 mmol) in ethanol (40 ml) was heated, under reflux, for 6 h. The cooled products were concentrated under reduced pressure and the residue was triturated with light petroleum (b.p. 60—80 °C) to give crude 4-methyl-2-(*p*-tolylthiomethylamino)pyrimidine (2.48 g, 61%).

Sodium borohydride (0.20 g, 5.4 mmol) was added over 15 min to a solution of the above product (0.366 g, 1.4 mmol) in ethanol (15 ml). The reactants were then heated, under reflux, for 1 h and the products were worked-up as described above in the preparation of *p*-chloro-*N*-(n-propyl)aniline except that ethyl acetate was used in the final extractions. Crystallization of the product from ethyl acetate gave 4-methyl-2-methylaminopyrimidine (Found: C, 57.5; H, 7.35; N, 33.9. Calc. for $C_6H_9N_3 \cdot 0.1H_2O$: C, 57.7; H, 7.4;

N, 33.6%) (0.164 g, 89%), m.p. 54—55 °C (lit.,[14] 55—56 °C); $M^+$, 123 (100%); $\delta_H$ [$(CD_3)_2SO$–$D_2O$] 2.27 (3 H, s), 2.82 (3 H, s), 6.49 (1 H, d, *J* 5.0 Hz), and 8.12 (1 H, d, *J* 5.0 Hz).

2-*Methylaminothiazole* (10b).—A solution of 2-aminothiazole (2.0 g, 20 mmol), aqueous formaldehyde (*ca.* 39% w/v, 1.5 ml, 19.5 mmol), and *p*-thiocresol (2.48 g, 20 mmol) in ethanol (50 ml) was heated, under reflux, for 2 h. After the cooled products had been concentrated under reduced pressure, the residue was triturated with light petroleum (b.p. 60—80 °C) and filtered to give 2-(*p*-tolylthiomethyl)-aminothiazole, m.p. 52—54 °C (3.80 g, 80%).

Sodium borohydride (0.047 g, 1.3 mmol) was added to a solution of the above product (0.30 g, 1.3 mmol) in 1,2-dimethoxyethane (3 ml). The reactants were then heated, under reflux, for 45 min and the products were worked up as described above in the preparation of *p*-chloro-*N*-(n-propyl)aniline, except that ethyl acetate was used in the final extractions, to give 2-methylaminothiazole (0.138 g, 95%) as a colourless oil. A solution of this material (0.10 g, 0.88 mmol) in ethanol (2 ml) was treated with saturated alcoholic picric acid (2 ml). Recrystallization of the precipitated product from ethanol gave 2-*methylaminothiazole picrate* [Found (in material dried *in vacuo* at 90 °C): C, 36.2; H, 3.2; N, 19.1 $C_{10}H_9N_5O_7S{\cdot}0.5C_2H_5OH$ requires C, 36.1; H, 3.3; N, 19.1%], (0.288 g, 96%), m.p. 190 °C (decomp.); $\delta_H$ [$(CD_3)_2SO$–$D_2O$] 3.01 (3 H, s), 6.95 (1 H, d, *J* 4.4 Hz), 7.31 (1 H, d, *J* 4.4 Hz), and 8.65 (2 H, s).

2-(*n-Propylamino*)*thiazole* (10c).—A solution of 2-aminothiazole (4.0 g, 40 mmol), propionaldehyde (3.4 ml, 47 mmol) and *p*-thiocresol (5.46 g, 44 mmol) in ethanol (100 ml) was heated, under reflux, for 2 h. The cooled products were concentrated under reduced pressure and the residue was redissolved in 1,2-dimethoxyethane (35 ml). Sodium borohydride (1.50 g, 40.5 mmol) was added over a period of 10 min to the latter solution and the reactants were then heated, under reflux, for 90 min. The products were worked up according to the procedure described above in the preparation of *p*-chloro-*N*-(n-propyl)aniline to give 2-(n-propylamino)thiazole as a colourless oil (4.6 g, 81%). A solution of this material (1.00 g, 7 mmol) in ethanol (10 ml) was treated with a saturated alcoholic solution of picric acid (15 ml). Recrystallization of the resulting precipitate from ethanol gave 2-(*n-propylamino*)*thiazole picrate* (Found: C, 38.8; H, 3.65; N, 18.7. $C_{12}H_{13}N_5O_7S$ requires C, 38.8; H, 3.5; N, 18.9%), (2.32 g, 89%), m.p. 153—154 °C; $\delta_H$ [$(CD_3)_2SO$–$D_2O$] 0.95 (3 H, t, *J* 7.4 Hz), 1.64 (2 H, m), 3.31 (2 H, t, *J* 6.8 Hz), 6.95 (1 H, d, *J* 4.6 Hz), 7.30 (1 H, d, *J* 4.6 Hz), and 8.64 (2 H, s).

2-*Methylaminobenzimidazole* (12b).—A solution of 2-aminobenzimidazole (1.05 g, 7.9 mmol), aqueous formaldehyde (*ca.* 39% w/v; 1.2 ml, 15.6 mmol), and *p*-thiocresol (1.96 g, 15.7 mmol) in ethanol (30 ml) was heated, under reflux, for 7 h. The cooled products were filtered and the residue was washed with chloroform. Recrystallization of this material from ethanol gave 2-(*p*-tolylthiomethylamino)-benzimidazole, m.p. 156—158 °C (1.86 g, 87%).

Sodium borohydride (1.00 g, 27 mmol) was added over a period of 10 min to a solution of the above product (0.96 g, 3.6 mmol) in ethanol (40 ml) and the reactants were then heated, under reflux, for 35 min. The products were worked up according to the procedure described above in the preparation of *p*-chloro-*N*-(n-propyl)aniline, except that ethyl acetate was used in the final extractions to give 2-*methylaminobenzimidazole* {Found [in material recrystallized from ethyl acetate–light petroleum (b.p. 60—80 °C) and dried *in vacuo* at 80 °C]: C, 65.0; H, 6.2; N, 28.2. $C_8H_9N_3$ requires C, 65.3; H, 6.2; N, 28.5%} (0.401 g, 76%), m.p. 167—168 °C; $M^+$, 147 (100%); $\delta_H$ [$(CD_3)_2CO$] 3.02 (3 H, s), 6.90 (2 H, m), and 7.18 (2 H, m); $\delta_C$ [$(CD_3)_2SO$] 29.12. 111.51, 119.01, 138.83, and 156.31; $\lambda_{max.}$ (95% EtOH) 287 and 247 (ε 10 000 and 7 800), $\lambda_{min.}$ 261 and 234 nm (ε 1 300 and 5 200).

2-(*n-Propylamino*)*benzimidazole* (12c).—A solution of 2-aminobenzimidazole (1.50 g, 11.3 mmol), propionaldehyde (1.5 ml, 14.8 mmol), and *p*-thiocresol (2.00 g, 16.0 mmol) in ethanol (20 ml) was heated, under reflux, for 3 h. The products were concentrated under reduced pressure and the resulting oil was triturated with light petroleum (b.p. 60—80 °C) to give 2-[1-(*p*-tolylthio)propylamino]benzimidazole as a pale brown glass (2.67 g, 80%).

Sodium borohydride (0.537 g, 14.5 mmol) was added over a period of 10 min to a solution of the above material (0.87 g, 2.9 mmol) in ethanol (40 ml) and the reactants were then heated, under reflux, for 45 min. The products were worked up as described in the preparation of *p*-chloro-*N*-(n-propyl)aniline, except that ethyl acetate was used in the final extraction. Chromatography of the product on silica gel gave 2-(*n-propylamino*)*benzimidazole* [Found (in material dried *in vacuo* at 70 °C): C, 68.2; H, 7.4; N, 23.75. $C_{10}H_{13}N_3$ requires C, 68.5; H, 7.5; N, 24.0%] as a crystalline solid, m.p. 140 °C (0.32 g, 65%); $\delta_H$ [$(CD_3)_2SO$–$D_2O$] 0.93 (3 H, t, *J* 7.5 Hz), 1.58 (2 H, m), 3.25 (2 H, t, *J* 7.1 Hz), 6.90 (2 H, m), and 7.16 (2 H, m); $\delta_C$ [$(CD_3)_2SO$] 11.53, 22.79, 44.13, 111.62, 119.25, 138.66, and 155.66.

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REFERENCES

[1] R. H. Hall, 'The Modified Nucleosides in Nucleic Acids,' Columbia University Press, New York and London, 1971.
[2] P. K. Bridson and C. B. Reese, *Bioorganic Chem.*, 1979, **8**, 339.
[3] Ö. Kemal and C. B. Reese, *Synthesis*, 1980, 1025.
[4] A. S. Tomcufcik and L. N. Starker in 'Pyridine and Its Derivatives,' Part III, ed. E. Klingsberg, Interscience, New York, 1962, pp. 28 *et seq.*
[5] G. R. Grillot and R. E. Schaffrath, *J. Org. Chem.*, 1959, **24**, 1035.
[6] J. H. Billman and A. C. Diesing, *J. Org. Chem.*, 1957, **22**, 1068.
[7] M. L. Moore, *Organic React.*, 1949, **5**, 301.
[8] R. F. Borch and A. I. Hassid, *J. Org. Chem.*, 1972, **37**, 1673.
[9] S. B. Kadin, *J. Org. Chem.*, 1973, **38**, 1348.
[10] 'Handbook of Chemistry and Physics,' 55th edn., ed. R. C. Weast, CRC Press, Cleveland, 1974, p. C-111.
[11] 'Dictionary of Organic Compounds,' eds. J. R. A. Pollock and R. Stevens, Eyre and Spottiswoode, London, 1965, p. 1407.
[12] F. W. Bergstrom, H. G. Sturz, and H. W. Tracey, *J. Org. Chem.*, 1946, **11**, 239.
[13] J. P. Wibaut and F. W. Broekman, *Recl. Trav. Chim., Pays-Bas.*, 1961, **80**, 309.
[14] D. J. Brown and M. N. Paddon-Row, *J. Chem. Soc. C*, 1967, 1928.