The Structures of Di-*N*-Aroyl Derivatives of Adenosine and 2-Aminopyridine

By **P. Anne Lyon** and **Colin B. Reese,*** † University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW

2',3',5'-Tri-*O*-acetyladenosine (4a) and 2-aminopyridine (6a) both undergo di-*N*-aroylation on their exocyclic nitrogen atoms.

THREE of the four main bases of nucleic acids [cytosine (1a), adenine (2a), and guanine (3a)] have potentially tautomeric amidine systems as a structural feature and hence the possibility exists of their giving rise to isomeric monoacyl derivatives. The site of acylation is a matter of importance as the derived nucleosides and nucleotides are usually protected by *N*-acylation for the purposes of oligonucleotide synthesis.[1] Appropriate studies [2-4] have indicated that such nucleoside and nucleotide derivatives undergo acylation on their exocyclic nitrogen atoms. The same conclusion has been reached for 2-aminopyridine [5] (6a).

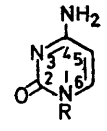
Cytidine [6] (1; R = β-D-ribofuranosyl), adenosine [7] (2; R = β-D-ribofuranosyl), and 2-aminopyridine [5] (6a) also form di-*N*-benzoyl derivatives but none of the structures of these systems has been established. The pentabenzoyl derivatives of cytidine [6] and adenosine [7] have been formulated as *N*(3),*N*(4)- and *N*(1),*N*(6)-diacyl systems, respectively. Indeed, although several authors [8] have alluded to the possibility of alternative structures, di-*N*-acyl derivatives of adenosine and its nucleotides have been generally formulated as *N*(1),*N*(6)-diacyl compounds [such as (5a)]. Structure (7a) has been advocated [9] for the dibenzoyl derivative of 2-aminopyridine (6a) but the alternative structure (6d) has also been used.[10] However, 2-aminopyridine has been shown [11] to form *N*(1),*N*(2)-bisarylsulphonyl derivatives (7; $R^1 = ArSO_2$, $R^2 = Ar'SO_2$) which readily rearrange to the corresponding *N*(2),*N*(2)-isomers (6; $R^1 = ArSO_2$, $R^2 = Ar'SO_2$). We now report that both adenosine and 2-aminopyridine undergo *NN*-diaroylation exclusively on their exocyclic nitrogen atoms. Since the completion of this work, Anzai and Matsui [12] have reported similar conclusions regarding the aroylation of adenosine derivatives and of 9-methyladenine.

The reaction between 2',3',5'-tri-*O*-acetyladenosine (4a) and *p*-toluoyl chloride (2·2 mol. equiv.) in pyridine solution at room temperature gave an *NN*-di-*p*-toluoyl derivative as the sole nucleoside product. This compound, isolated crystalline in 56% yield, has been assigned the structure (4d) on the basis of the single

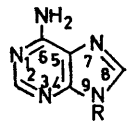
† *Present address:* Department of Chemistry, King's College London, Strand, London WC2R 2LS.

[1] For example, see R. Lohrmann, D. Söll, H. Hayatsu, E. Ohtsuka, and H. G. Khorana, *J. Amer. Chem. Soc.*, 1966, **88**, 819.
[2] G. W. Kenner, C. B. Reese, and Sir Alexander Todd, *J. Chem. Soc.*, 1955, 855.
[3] G. B. Chheda and R. H. Hall, *J. Org. Chem.*, 1969, **34**, 3492.
[4] C. B. Reese and R. Saffhill, *J.C.S. Perkin I*, 1972, 2937.
[5] A. E. Tschitschibabin and J. G. Bylinkin, *Chem. Ber.*, 1922, **55**, 998.
[6] D. M. Brown, Sir Alexander Todd, and S. Varadarajan, *J. Chem. Soc.*, 1956, 2384.
[7] H. R. Bentley, K. G. Cunningham, and F. S. Spring, *J. Chem. Soc.*, 1951, 2301.
[8] For example, see M. Smith, D. H. Rammler, I. H. Goldberg, and H. G. Khorana, *J. Amer. Chem. Soc.*, 1962, **84**, 430; S. Chládek, J. Žemlička, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1966, **31**, 1785.
[9] S. J. Angyal, W. O. Morris, and W. K. Warburton, *Austral. J. Sci. Res.*, 1952, *A***5**, 368.
[10] E. H. Huntress and H. C. Walter, *J. Org. Chem.*, 1948, **13**, 735.
[11] H. Dorn and G. Hilgetag, *Chem. Ber.*, 1964, **97**, 695.
[12] K. Anzai and M. Matsui, *Bull. Chem. Soc. Japan*, 1973, **46**, 3228.

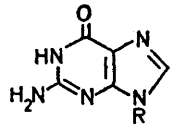
narrow resonance observed for methyl protons in its ^{1}H n.m.r. spectrum [in $CDCl_3$: τ 7·68 (6H, s, $W_{\frac{1}{2}}$ *ca.* 4 Hz); in C_6D_6: 8·16 (6H, s, $W_{\frac{1}{2}}$ *ca.* 3·5 Hz)]. It is noteworthy that the band-widths ($W_{\frac{1}{2}}$) of the methyl proton resonances of mono-*p*-toluoyl derivatives, such as *N*(6)-*p*-toluoyl-2′,3′,5′-tri-*O*-acetyladenosine (4c), also



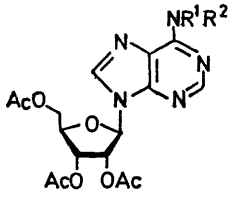
(1) a; R = H



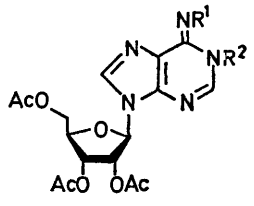
(2) a; R = H



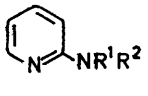
(3) a; R = H



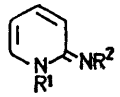
(4) a; $R^1 = R^2 = H$
b; $R^1 = H, R^2 = Bz$
c; $R^1 = H, R^2 = p\text{-}MeC_6H_4\cdot CO$
d; $R^1 = R^2 = p\text{-}MeC_6H_4\cdot CO$
e; $R^1 = Bz, R^2 = p\text{-}MeC_6H_4\cdot CO$



(5) a; $R^1 = R^2 = p\text{-}MeC_6H_4\cdot CO$



(6) a; $R^1 = R^2 = H$
b; $R^1 = H, R^2 = Bz$
c; $R^1 = H, R^2 = p\text{-}MeC_6H_4\cdot CO$
d; $R^1 = R^2 = Bz$
e; $R^1 = R^2 = p\text{-}MeC_6H_4\cdot CO$
f; $R^1 = Bz, R^2 = p\text{-}MeC_6H_4\cdot CO$



(7) a; $R^1 = R^2 = Bz$

appear to be in the range 3·5—4 Hz (see Experimental section). The addition of $Pr(fod)_3$ [13] to the solution of (4d) in deuteriochloroform caused the methyl protons to resonate at slightly higher field but the signal remained a sharp singlet with no detectable increase in band-width. In dideuteriodichloromethane solution at −85°, the methyl protons of (4d) resonated as a singlet, but there was an appreciable increase in band-width. Finally, the ^{13}C n.m.r. spectrum of (4d) was observed to display only one signal attributable to a methyl carbon atom.

Although it seemed likely from the above n.m.r. data that the *NN*-di-*p*-toluoyl derivative of 2′,3′,5′-tri-*O*-acetyladenosine was indeed (4d), the evidence was inconclusive since the methyl signals of the isomeric *N*(1),*N*(6)-di-*p*-toluoyl derivative (5a) might also be coincident. However, the structural assignment was confirmed as follows. *N*(6)-Benzoyl- and *N*(6)-*p*-toluoyl-2′,3′,5′-tri-*O*-acetyladenosines (4b and c) were treated with slight excesses of *p*-toluoyl and benzoyl chlorides, respectively, in pyridine solution at room temperature. The same compound, which must therefore be the *N*(6),*N*(6)-diacyl derivative (4c), was obtained in high yield as the sole nucleoside product in each experiment; it was isolated, following adsorption chromatography, as a colourless glass in 87 and 79% yield, respectively. Pure *N*(6)-benzoyl-*N*(6)-*p*-toluoyl-2′,3′,5′-tri-*O*-acetyladenosine (4e) was obtained as a crystalline hemihydrate (76% recovery) from one portion of the glassy material. The crystalline and glassy materials obtained from the two experiments had identical t.l.c. and spectroscopic (i.r., ^{1}H n.m.r., and mass) properties. It is important to be able to account for most, if not all, of the material obtained in both experiments if the possibility that mixtures of isomers are formed, is to be excluded. For this reason, the present studies with 2′,3′,5′-tri-*O*-acetyladenosine (4a) add considerable weight to Anzai and Matsui's conclusions,[12] based on their experiments with 9-methyladenine.*

Diaroylation of 2-aminopyridine (6a) was shown, in the same way, to lead solely to *N*(2),*N*(2)-diaroyl derivatives. Thus (6e) was obtained as the sole product from 2-aminopyridine and an excess of *p*-toluoyl chloride in pyridine solution; it was isolated as a pure crystalline solid in 85% yield and characterized as the *N*(2),*N*(2)-di-*p*-toluoyl derivative in the same way (see Experimental section) as the adenosine derivative (4d). Similarly, 2-(benzoyl-*p*-toluoylamino)pyridine (6f) was obtained, in virtually quantitative yield, either by treating 2-benzamidopyridine (6b) with a slight excess of *p*-toluoyl chloride or 2-*p*-toluamidopyridine (6c) with a slight excess of benzoyl chloride; it was isolated as colourless needles, in 85% yield, from the products of both reactions. When 2-aminopyridine (6a) was treated with a stoicheiometric amount of either benzoyl or *p*-toluoyl chloride, in pyridine solution, the *N*(2)-monoaroyl derivative obtained (6b or c) was contaminated with some *N*(2),*N*(2)-diaroyl derivative (6d or e). The latter contaminants could be removed readily by treating the products with aqueous sodium hydroxide before work-up.

Although it is not justifiable to generalize from the above results, 2′,3′,5′-tri-*O*-acetyladenosine and 2-aminopyridine are dissimilar enough for us to conclude that the reaction between aroyl chlorides and related heterocyclic amino-compounds (*e.g.* cytidine) will most likely lead to products in which both acyl groups are attached to the exocyclic nitrogen atom. By analogy with the arylsulphonylation of 2-aminopyridine,[11] it is possible that *NN*′-diaroyl derivatives [such as (5a)] are formed first and then rearrange.

* The conclusions of these workers were based on the isolation of a glassy material, containing carbon tetrachloride, in *ca.* 20% yield, from the reaction between *N*(6)-*p*-toluoyl-9-methyladenine and benzoyl chloride, and of a non-crystalline product, in *ca.* 32% yield, from the reaction between *N*(6)-benzoyl-9-methyladenine and *p*-toluoyl chloride.

[13] R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, 1971, **93**, 1522.

EXPERIMENTAL

^{1}H N.m.r. spectra were measured at 100 MHz with a Varian HA-100 spectrometer (tetramethylsilane used as internal standard). ^{13}C N.m.r. spectra were measured at 25·2 MHz with a Varian XL-100 spectrometer; deuteriochloroform was used as internal standard and chemical shifts are given in p.p.m. downfield from tetramethylsilane. Mass spectra were recorded with an A.E.I. MS9 spectrometer, i.r. spectra with a Perkin-Elmer 257 G spectrometer, and u.v. spectra with a Pye Unicam SP 1800 recording spectrophotometer.

Thin-layer chromatograms were run on glass plates coated with Merck Kieselgel F_{254} in the following solvent systems: (A) $CHCl_3$–MeOH (90 : 10 v/v), (B) $CHCl_3$–MeOH (95 : 5 v/v), (C) $CHCl_3$. Reeve Angel Silica Gel/CT was used for short column chromatography.[14] Pyridine was dried by heating under reflux with calcium hydride and then distilled.

2′,3′,5′-*Tri*-O-*acetyladenosine* (4a).—Adenosine (5·34 g, 20 mmol), acetic anhydride (11·4 ml, 121 mmol), and anhydrous pyridine (50 ml) were stirred together at 20°. After 16 h, methanol (20 ml) was added and, after a further 1 h, the products were concentrated under reduced pressure. The gum so obtained was dissolved in ethanol and the solution evaporated. This process was repeated and the residual glass was recrystallized from ethanol to give colourless crystals (7·2 g, 92%), m.p. 171—172° (lit.,[15] 174°). T.l.c. [system (A)] indicated that the crystals were contaminated with *ca.* 5% of a higher R_F (0·55) component. Pure 2′,3′,5′-tri-*O*-acetyladenosine [R_F 0·48, system (A)], m.p. 174°, was obtained by short column chromatography.

N(6),N(6)-*Di*-p-*toluoyl*-2′,3′,5′-*tri*-O-*acetyladenosine* (4d).—*p*-Toluoyl chloride (3·4 g, 22 mmol) was added to a stirred solution of 2′,3′,5′-tri-*O*-acetyladenosine (3·93 g, 10 mmol) in anhydrous pyridine (50 ml) at 20°. After 16 h the products were poured onto ice (400 g). The precipitate was filtered off and dissolved in chloroform (100 ml), and the solution was extracted with ice-cold saturated aqueous sodium hydrogen carbonate (100 ml). The chloroform layer was dried ($MgSO_4$) and concentrated under reduced pressure, and the residual gum dissolved in ethanol. Evaporation gave a glass which was kept *in vacuo* (P_2O_5) at 20° for 16 h. Short column chromatography [400 g silica gel; $CHCl_3$–MeOH (99 : 1 v/v)] gave a glass which crystallized from ethanol–water (2 : 1 v/v) to give the N(6),N(6)-*di*-p-*toluoyl derivative* (3·50 g, 56%) (Found: C, 60·9; H, 5·1; N, 10·9. $C_{32}H_{31}N_5O_9$ requires C, 61·0; H, 4·9; N, 11·1%), m.p. 100—101°; R_F 0·63 [system (B)]; $\lambda_{max.}$ (95% EtOH) 262 (ε 28,300), $\lambda_{infl.}$ 270 (27,600), $\lambda_{min.}$ 233 nm (12,400); τ($CDCl_3$) 1·38 (1H, s), 1·83 (1H, s), 2·27 (4H, d, *J* 8 Hz), 2·87 (4H, d, *J* 8Hz), 3·77 (1H, d, *J* 5·5 Hz), 4·07 (1H, m), 4·33 (1H, m), 5·59 (3H, m), 7·68 (6H, s, $W_{\frac{1}{2}}$ *ca.* 4 Hz), and 7·94 (9H, s); addition of Pr(fod)$_3$[13] (0·025 g) to a solution of (4d) (0·03 g) in $CDCl_3$ (0·4 ml) shifted the two highest field signals to τ 7·73 (6H, s, $W_{\frac{1}{2}}$ *ca.* 4 Hz), 8·02 (3H, s), 8·36 (3H, s), and 8·75 (3H, s); τ(C_6D_6) 8·16 (6H, s, $W_{\frac{1}{2}}$ *ca.* 3·5 Hz), 8·35 (3H, s), 8·40 (3H, s), and 8·42 (3H, s); τ(CD_2Cl_2) at 20° 7·67 (6H, s) and at −85° 7·61 (6H, s, $W_{\frac{1}{2}}$ *ca.* 6 Hz); δ_C ($CDCl_3$) 21·7 (s); M^+ 629.

N(6)-*Benzoyl*-2′,3′,5′-*tri*-O-*acetyladenosine* (4b)—*N*(6)-Benzoyladenosine (1·484 g, 4·0 mmol), acetic anhydride (1·346 g, 13·2 mmol), and anhydrous pyridine (25 ml) were stirred together at 20°. After 16 h methanol (4 ml) was added and, after a further 1 h, the products were concentrated under reduced pressure. The residual gum was dissolved in ethanol and the solution evaporated. This process was repeated and the resultant material was purified by short column chromatography [150 g silica gel; $CHCl_3$–MeOH (79 : 1 v/v)] to give a glass which crystallized from ethanol–water (1 : 1 v/v) affording N(6)-*benzoyl*-2′,3′,5′-*tri*-O-*acetyladenosine monohydrate* (1·68 g, 82%) [Found (material dried *in vacuo* over P_2O_5 at 45°): C, 53·4; H, 5·0; N, 13·7. $C_{23}H_{23}N_5O_8,H_2O$ requires: C, 53·6; H, 4·85; N, 13·6%], m.p. 88—89°; R_F 0·49 [system (B)]; $\lambda_{max.}$ (95% EtOH) 234 and 280 (ε 11,000 and 19,800), $\lambda_{min.}$ 226 and 247 nm (10,700 and 9600); τ($CDCl_3$) 1·26 (1H, s), 1·82 (1H, s), 1·92—2·54 (5H, m), 3·74 (1H, d, *J* 5 Hz), 4·04 (1H, t, *J* 5 Hz), 4·33 (1H, m), 5·35 (2H, s), 5·57 (3H, m), 7·87 (3H, s), 7·90 (3H, s), and 7·94 (3H, s); M^+ 497.

N(6)-p-*Toluoyladenosine*.—Adenosine (2·67 g, 10·0 mmol), *p*-toluoyl chloride (8·5 g, 55·0 mmol), and anhydrous pyridine (25 ml) were stirred together at 20°. After 16 h the products were poured onto ice (150 g). The precipitate was filtered off and dissolved in chloroform. The solution was washed with water, dried, and evaporated to give a gum * [R_F 0·65 in system (B)]. This was dissolved in ethanol (50 ml) and pyridine (16 ml) and treated with aqueous 10% sodium hydroxide (30 ml) at 20° for 5 min. The reaction was then quenched by addition of ethanol–acetic acid (1 : 3 v/v; 50 ml) followed by glacial acetic acid (32 ml). The products were concentrated under reduced pressure and the residue extracted with ether (5 × 100 ml). The remaining solid was crystallized from water to give N(6)-p-*toluoyladenosine hemihydrate* (2·90 g, 74%) [Found (material dried *in vacuo* over P_2O_5 at 100°): C, 55·2; H, 5·0; N, 17·7. $C_{18}H_{19}N_5O_5,0·5H_2O$ requires: C, 54·8; H, 5·1; N, 17·8%], m.p. 140—141°; R_F 0·23 [system (A)]; $\lambda_{max.}$ (95% EtOH) 282 (ε 23,600), $\lambda_{infl.}$ 262 (15,000), $\lambda_{min.}$ 233 nm (10,000), τ[$(CD_3)_2SO$–D_2O] 1·33 (1H, s), 1·36 (1H, s), 2·06 (2H, d, *J* 8 Hz), 2·70 (2H, d, *J* 8 Hz), 3·94 (1H, d, *J* 5 Hz), 5·37 (1H, t, *J* 5 Hz), 5·78 (1H, t, *J* 5 Hz), 5·98 (1H, m), 6·34 (2H, m), and 7·61 (3H, s, $W_{\frac{1}{2}}$ *ca.* 4 Hz); M^+ 385.

N(6)-p-*Toluoyl*-2′,3′,5′-*tri*-O-*acetyladenosine* (4c).—*N*(6)-*p*-Toluoyladenosine hemihydrate (0·394 g, 1·0 mmol), acetic anhydride (0·337 g, 3·3 mmol), and anhydrous pyridine (10 ml) were stirred together at 20°. After 16 h methanol (1 ml) was added and, after a further 1 h, the products were concentrated under reduced pressure. The residual gum was dissolved in ethanol and the solution evaporated. This process was repeated and the resultant material was purified by short column chromatography [50 g silica gel; $CHCl_3$–MeOH (79 : 1 v/v)] to give a glass which crystallized from ethanol–water (1 : 1 v/v) yielding N(6)-p-*toluoyl*-2′,3′,5′-*tri*-*O*-*acetyladenosine hemihydrate* (0·429 g, 83%) [Found (material dried *in vacuo* over P_2O_5 at 45°): C, 55·4; H, 4·9; N, 13·6. $C_{24}H_{25}N_5O_8,0·5H_2O$ requires C, 55·4; H, 5·0; N, 13·5%], m.p. 77—78°; R_F 0·50 [system (B)]; $\lambda_{max.}$ (95% EtOH) 282 (ε 23,400), $\lambda_{infl.}$ 262 (15,200), $\lambda_{min.}$ 232 nm (9300); τ [$(CD_3)_2SO$] 1·29 (1H, s), 1·38 (1H, s), 2·04 (2H, d, *J* 8 Hz), 2·69 (2H, d, *J* 8 Hz), 3·64 (1H, d, *J* 6 Hz), 3·91 (1H, m), 4·30 (1H, m), 5·60 (3H, m), 7·59 (3H, s, $W_{\frac{1}{2}}$ *ca.* 3·5 Hz), 7·88 (3H, s), 7·96 (3H, s), and 7·99 (3H, s); M^+ 511.

* This material could be crystallized from ethanol; it is believed to be *N*(6),*N*(6),*O*(2′),*O*(3′),*O*(5′)-penta-*p*-toluoyladenosine.

[14] B. J. Hunt and W. Rigby, *Chem. and Ind.*, 1967, 1868.
[15] H. Bredereck and A. Martini, *Chem. Ber.*, 1947, **80**, 401.

N(6)-*Benzoyl*-N(6)-p-*toluoyl*-2′,3′,5′-*tri*-O-*acetyladenosine* (4e).—(*a*) *p*-Toluoyl chloride (0·927 g, 6·0 mmol) was added to a stirred solution of *N*(6)-benzoyl-2′,3′,5′-tri-*O*-acetyladenosine monohydrate (1·03 g, 2·0 mmol) in anhydrous pyridine (10 ml) at 20°. After 3 h the products were poured onto ice (100 g) and the precipitate was filtered off and dissolved in chloroform (25 ml). The solution was extracted with ice-cold saturated aqueous sodium hydrogen carbonate (25 ml). The dried ($MgSO_4$) solution was concentrated under reduced pressure and the gum obtained kept *in vacuo* (P_2O_5) at 20° for 16 h before short column chromatography [100 g silica gel; $CHCl_3$–MeOH (99 : 1 v/v)]. A sample (0·35 g) of the resulting glass (1·07 g) was crystallized from ethanol–water (1 : 2 v/v; 36 ml) to give N(6)-*benzoyl*-N(6)-p-*toluoyl*-2′,3′,5′-*tri*-O-*acetyladenosine hemihydrate* [Found (material dried *in vacuo* over P_2O_5 at 55°): C, 59·7; H, 4·8; N, 11·0. $C_{31}H_{29}N_5O_9,0·5H_2O$ requires C, 59·6; H, 4·8; N, 11·2%], m.p. 90—91°; yield * 0·308 g [this corresponds to a yield of 0·942 g (76%) of crystalline material from 1·07 g of glass]; R_F 0·63 [system (B)]; $\lambda_{max.}$ (95% EtOH) 258 (ε 24,900), $\lambda_{infl.}$ 271 (23,400), $\lambda_{min.}$ 232 nm (13,800); $\nu_{max.}$ ($CHCl_3$) 3050m, 1750s, 1705s, 1600s, 1580s, 1492m, 1450m, and 1372m cm^{-1}; τ[$(CD_3)_2SO$] 1·28 (1H, s), 1·36 (1H, s), 2·21—2·84 (9H, m), 3·65 (1H, d, *J* 5·5 Hz), 3·98 (1H, t, *J* 5·5 Hz), 4·33 (1H, t, *J* 5 Hz), 5·63 (3H, m), 7·69 (3H, s, $W_{\frac{1}{2}}$ *ca.* 4 Hz), 7·92 (3H, s), 7·98 (3H, s), and 8·06 (3H, s); M^+ 615. Before crystallisation the glass showed $\lambda_{max.}$ (95% EtOH) 258 (ε 23,200), $\lambda_{infl.}$ 271 (21,700), $\lambda_{min.}$ 233 nm (14,200). The i.r., n.m.r., and mass spectra of the glass and crystalline material were identical.

(*b*) Benzoyl chloride (0·309 g, 2·2 mmol) was added to a stirred solution of *N*(6)-*p*-toluoyl-2′,3′,5′-tri-*O*-acetyladenosine hemihydrate (0·52 g, 1·0 mmol) in anhydrous pyridine (5 ml) at 20°. After 3 h the products were poured onto ice (50 g) and worked up as in (*a*). After short column chromatography (60 g silica gel) of the products a glass (0·485 g) was obtained. Crystallization of a sample (0·35 g) from ethanol–water (1 : 2 v/v) gave *N*(6)-benzoyl-*N*(6)-*p*-toluoyl-2′,3′,5′-tri-*O*-acetyladenosine hemihydrate (Found: C, 59·8; H, 5·0; N, 10·95%), m.p. [and mixed m.p. with crystalline material obtained in experiment (*a*)] 90—91°; yield 0·269 g [corresponding to a yield of 0·373 g (60%) of crystalline material from 0·485 g of glass]; $\lambda_{max.}$ (95% EtOH) 258 (ε 24,900), $\lambda_{infl.}$ 271 (23,500), $\lambda_{min.}$ 232 nm (13,900); R_F 0·63 [system (B)]. The i.r., n.m.r., and mass spectra of both the crystalline material and the glass were identical with the corresponding spectra of the crystals and the glass obtained in (*a*).

2-(*Di*-p-*toluoylamino*)*pyridine* (6e).—*p*-Toluoyl chloride (1·36 g, 8·8 mmol) was added to a stirred solution of 2-aminopyridine (0·376 g, 4·0 mmol) in anhydrous pyridine (10 ml) at 20°. The solution was stirred for 16 h and then poured onto ice (120 g). The precipitate was filtered off and dissolved in chloroform (25 ml), and the solution extracted with ice-cold aqueous sodium hydrogen carbonate (25 ml). The dried ($MgSO_4$) organic layer was concentrated under reduced pressure and the residue crystallized from ethanol (40 ml) to give 2-(*di*-p-*toluoylamino*)*pyridine* [Found (material dried *in vacuo* over P_2O_5 at 90°): C, 76·4; H, 5·5; N, 8·2. $C_{22}H_{18}N_2O_2$ requires C, 76·4; H, 5·5; N, 8·5%] as pale yellow crystals (1·12 g, 85%), m.p. 162—163°; R_F 0·69 [system (B)] and 0·06 [system (C)]; $\lambda_{max.}$ (95% EtOH) 220 and 267 (ε 19,600 and 19,800), $\lambda_{min.}$ 237 nm (11,500); τ($CDCl_3$) 1·64—2·96 (12H, m), 7·71 (6H, s, $W_{\frac{1}{2}}$ *ca.* 4Hz); addition of $Eu(fod)_3$ (0·08 g) to a solution of (6e) (0·01 g) in $CDCl_3$ (0·4 ml) shifted the highest field signal to 7·61 (6H, s, $W_{\frac{1}{2}}$ *ca.* 4 Hz); τ(C_6D_6) 8·16 (6H, s, $W_{\frac{1}{2}}$ *ca.* 3·5 Hz); τ(CD_2Cl_2) at 20° 7·69 (6H, s), at −85° 7·65 (6H, s) and at −113° 7·65 (6H, s); δ_C ($CDCl_3$) 21·6 (s); M^+ 330.

2-p-*Toluamidopyridine* (6c).—*p*-Toluoyl chloride (3·09 g, 20 mmol) was added to a stirred solution of 2-aminopyridine (1·88 g, 20 mmol) in anhydrous pyridine (20 ml) at 20°. The solution was stirred for 16 h and then aqueous 10% sodium hydroxide (20 ml) was added. After a further 2 h the products were poured onto ice (150 g). The precipitate was filtered off and dissolved in chloroform (100 ml), and the solution washed with water (100 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The solid was redissolved in ethanol and the solution evaporated. Crystallization of this material from ethanol–water (1 : 1 v/v; 35 ml) gave 2-*p*-toluamidopyridine (3·95 g, 93%) [Found (material dried *in vacuo* over P_2O_5 at 80°): C, 73·7; H, 5·55; N, 13·4. Calc. for $C_{13}H_{12}N_2O$: C, 73·6; H, 5·7; N, 13·2%], m.p. 105—106° (lit.,[16] 107—108°); R_F 0·69 [system (B)] and 0·16 [system (C)]; $\lambda_{max.}$ (95% EtOH) 252 and 283 (ε 15,200 and 16,100), $\lambda_{min.}$ 224 and 270 nm (6500 and 13,400); τ($CDCl_3$) 0·84br (1H, s), 1·56—3·07 (8H, m), and 7·63 (3H, s, $W_{\frac{1}{2}}$ *ca.* 3·5 Hz); M^+ 212.

2-*Benzamidopyridine* (6b).—Benzoyl chloride (2·81 g, 20 mmol) was added to a stirred solution of 2-aminopyridine (1·88 g, 20 mmol) in anhydrous pyridine (10 ml) at 20°. The solution was stirred for 16 h, treated with aqueous 10% sodium hydroxide (20 ml) and worked up as in the preparation of 2-*p*-toluamidopyridine. Crystallization from ethanol–water (1 : 1 v/v; 30 ml) gave 2-benzamidopyridine (1·94 g, 49%) [Found (material dried *in vacuo* over P_2O_5 at 60°): C, 72·8; H, 5·2; N, 14·1. Calc. for $C_{12}H_{10}N_2O$: C, 72·7; H, 5·05; N, 14·1%], m.p. 80—81° (lit.,[10] 82—83°); R_F 0·69 [system (B)] and 0·16 [system (C)]; $\lambda_{max.}$ (95% EtOH) 253 and 282 (ε 11,700 and 13,700), $\lambda_{infl.}$ 242 (11,100), $\lambda_{min.}$ 222 and 265 nm (8300 and 11,000); τ($CDCl_3$) 0·74br (s) and 1·50—3·16 (m); M^+ 198.

2-(*Benzoyl*-p-*toluoylamino*)*pyridine* (6f).—(*a*) *p*-Toluoyl chloride (0·371 g, 2·4 mmol) was added to a stirred solution of 2-benzamidopyridine (0·396 g, 2·0 mmol) in anhydrous pyridine (5 ml) at 20°. The solution was stirred for 16 h and poured onto ice (50 g). The precipitate was filtered off and dissolved in chloroform (10 ml). The solution was extracted with ice-cold saturated aqueous sodium hydrogen carbonate (10 ml), dried ($MgSO_4$), and concentrated. Crystallization of a sample (0·35 g) of the solid (0·652 g) from ethanol (17 ml) gave 2-(*benzoyl*-p-*toluoylamino*)*pyridine* [Found (material dried in vacuo over P_2O_5 at 90°): C, 75·7; H, 5·25; N, 8·9. $C_{20}H_{16}N_2O_2$ requires C, 75·95; H, 5·1; N, 8·9%], needles, m.p. 168°; yield 0·287 g [this corresponds to a total yield of 0·535 g (85%) of crystalline material]; R_F 0·69 [system (B)] and 0·06 [system (C)]; $\lambda_{max.}$ (95% EtOH) 246 (ε 20,200), $\lambda_{infl.}$ 264 (18,700), $\lambda_{min.}$ 225 nm (14,500); $\nu_{max.}$ ($CHCl_3$) 3020m, 1687s, 1610m, 1590m, 1467m, and 1434m cm^{-1}; τ($CDCl_3$) 1·62—3·00 (13H, m) and 7·69 (3H, s, $W_{\frac{1}{2}}$ *ca.* 4Hz); M^+ 316. Before crystallization the material showed $\lambda_{max.}$ (95% EtOH) 246 (ε 20,200), $\lambda_{infl.}$ 264 (18,300), $\lambda_{min.}$ 225 nm (13,500). The i.r., n.m.r., and mass spectra of this material were not detectably changed by crystallization.

* A further 0·014 g of colourless solid was obtained by evaporation of the mother liquors.

[16] J. Mirek, *Zeszyty Nauk. Uniw. Jagiellon., Pr. Chem.*, 1965, No. 10, 61 (*Chem. Abs.*, 1967, **66**, 37,125h).

(*b*) Benzoyl chloride (0·336 g, 2·4 mmol) was added to a stirred solution of *p*-toluamidopyridine (0·424 g, 2·0 mmol) in anhydrous pyridine (5 ml) at 20°. After 16 h the products were poured onto ice (50 g) and worked up as in (*a*) to give a solid (0·649 g). Crystallization of a sample (0·35 g) from ethanol gave 2-(benzoyl-*p*-toluoylamino)-pyridine (Found: C, 76·1; H, 5·3; N, 8·6%), m.p. [and mixed m.p. with crystalline material obtained in (*a*)] 168°; yield 0·289 g [corresponding to a total yield of 0·536 g (85%) of crystalline material]; R_F 0·69 [system (B)] and 0·06 [system (C)]; $\lambda_{max.}$ (95% EtOH) 246 (ε 19,900), $\lambda_{infl.}$ 264 (17,900), $\lambda_{min.}$ 225 nm (13,500); the i.r., n.m.r., and mass spectra of both the crystalline material and solid were identical with the corresponding spectra of the crystals and solid obtained in (*a*).

One of us (P. A. L.) thanks the S.R.C. and Girton College, Cambridge, for a Research Studentship and a Fellowship, respectively.

[4/1708 *Received*, 14*th August*, 1974]