Acylation of Heteroaromatic Amines. II Dibenzoylation of Aminopyridines.

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Three isomeric aminopyridines were reacted with an excess of benzoyl chloride in the presence of an excess of triethylamine, giving the corresponding dibenzoylaminopyridines in high yields. As an application of the dibenzoylation, the aminopyridines were also reacted with phthaloyl dichloride, resulting in appreciable yields of the respective *N*-pyridylphthalimides. The rate of the conversion under various conditions was studied with high pressure liquid chromatography in order to investigate the difference in reactivity among the three isomers.

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In the previous paper (1) we have reported that diaminopyridazines, whose amino groups are attached to the 3 and 6 positions, can readily be converted to the corresponding tetrabenzoylated derivatives by treatment with benzoyl chloride in the presence of triethylamine. Such perbenzoylation was considered to be characteristic of the amino group attached to the carbon atom α to the unsaturated nitrogen in heterocycles.

In the present work, similar perbenzoylation was applied to α-, β- and γ-aminopyridines in order to investigate differences in reactivity at the position to which the amino group is attached. Concerning dibenzoylation of aminopyridines, only that of α-aminopyridine has been reported (2) (3), whereas those of the β- and γ-isomers have never appeared in the literature. By treatment with an excess of benzoyl chloride in the presence of an excess of triethylamine in chloroform, it was found that not only α-but also β- and γ-aminopyridines were converted to the corresponding dibenzoylaminopyridines in high yields. As an application of dibenzoylation, α-, β- and γ-aminopyridines were also reacted with phthaloyl dichloride, resulting in appreciable yields of the corresponding *N*-pyridylphthalimides. These compounds can only be prepared under otherwise much more drastic conditions.

Scheme I

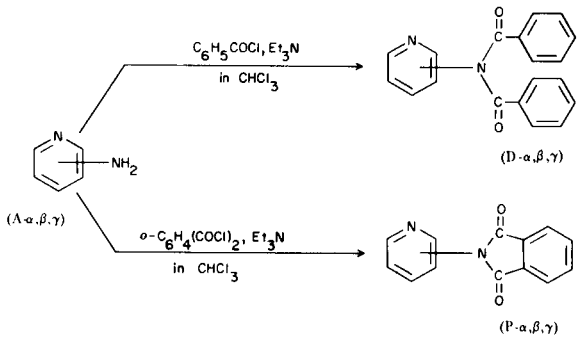

Table I

Reaction Products (a)

Product (b)	Recrystallization solvent	Crystal form	M.p. °C (c)	Yield %	Analyses: Calcd%, Found% C	H	N
D-α	hexane	white needles	166-167 (d)	93.4	75.50	4.64	9.27
					75.21	4.91	9.28
D-β	hexane	pale yellow needles	132-133	84.0	75.50	4.64	9.27
					75.46	4.38	9.02
D-γ	hexane-benzene	pale brown leaflets	168-169	87.2	75.50	4.64	9.27
					75.34	4.54	9.02
P-α	ethanol	white needles	225-226 (e)	60.4	69.64	3.57	12.50
					69.47	3.40	12.50
P-β	ethanol	orange needles	170-171 (f)	50.4	69.64	3.57	12.50
					69.55	3.31	12.61
P-γ	ethanol	pale orange needles	231-232 (g)	72.2	69.64	3.57	12.50
					69.89	3.59	12.75

(a) Each reaction was carried out with the molar ratio of A:B:T = 1:4:4 in chloroform under reflux. (b) Product letter corresponds to that in Scheme I; its Greek suffix means the position of the substituent. (c) Melting points were observed in a capillary and are uncorrected. (d) Lit. (2) m.p. 168-169°. (e) Lit. (4) m.p. 224°. (f) Melting point of the same product, which was prepared by the fusion reaction of phthalic anhydride with β-aminopyridine, is 171-172°. (g) Lit. (5) m.p. 232-233°.

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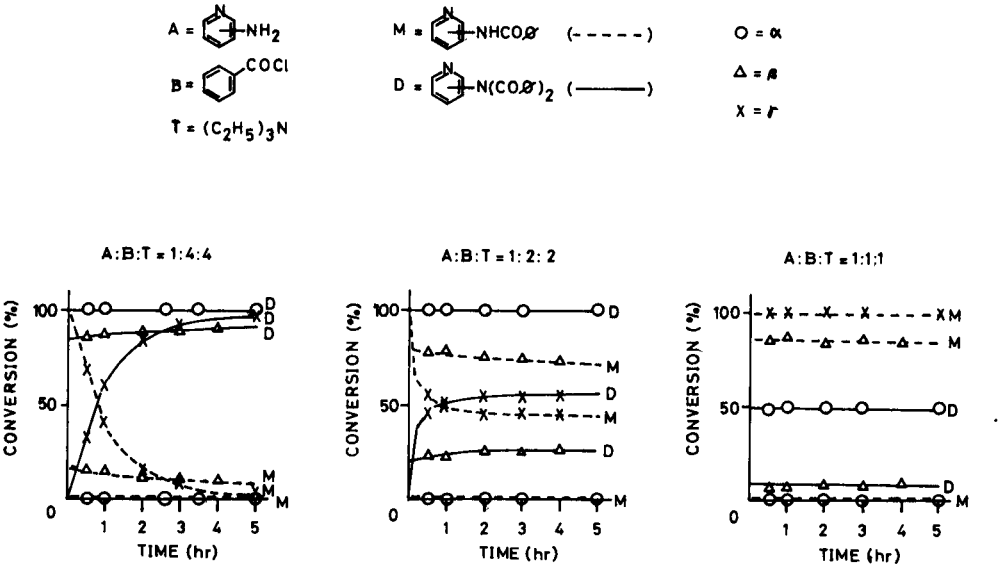

Figure I. Benzoylation of aminopyridines. Reaction condition; A: 1.0 mmole, solvent; chloroform (10 ml.), reaction temperature: 70°.

In order to investigate a difference in reactivity among three isomeric aminopyridines, the rate of the conversion under various conditions was studied with high pressure liquid chromatography (hplc).

Influence of the Molar Ratio of the Reactants.

The reaction of aminopyridine (A) with benzoyl chloride (B) in the presence of triethylamine (T) was carried out in chloroform at its refluxing temperature, with the initial molar ratios of A:B:T = 1:4:4, 1:2:2 and 1:1:1, respectively. The mono- and di-benzoylated products in the reaction mixture were detected by hplc with the lapse of time. The results are shown in Figure I.

Figure I indicates that α-aminopyridine has an extremely high convertibility with respect to dibenzoylation, since all cases of A:B:T ratios indicated complete dibenzoylation at an early stage in the reaction. On the other hand, β- and γ-aminopyridines were dibenzoylated gradually with the lapse of reaction time, except in the case of A:B:T = 1:1:1, where benzoyl chloride seemed to be consumed predominantly in monobenzoylation.

Effect of Triethylamine on Dibenzoylation.

In the absence of triethylamine, aminopyridine was reacted with benzoyl chloride (A:B = 1:4) in chloroform at its refluxing temperature for 4 hours. Four times a molar excess of triethylamine to initial moles of aminopyridine was immediately added, and the reaction was continued for another 4 hours. The conversion rates are shown in Figure II.

From Figure II, it can be said that, in the absence of triethylamine, β- and γ-aminopyridines form only mono-

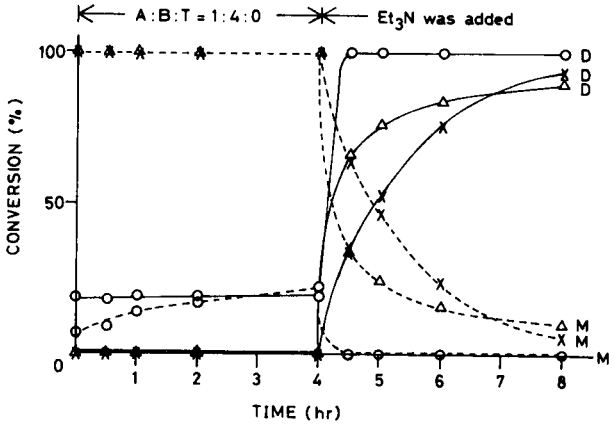

Figure II. Benzoylation of aminopyridines in the absence and following addition of triethylamine (T = 4). Letters, A, B, T, M, D, α, β and γ are same as those in Figure I. Reaction condition; A: 1.0 mmole, solvent: chloroform (10 ml.), reaction temperature: 70°.

benzoylated products in spite of the presence of excess benzoyl chloride, while the α-isomer is, to some extent, dibenzoylated. By the following addition of triethylamine, the residual benzoyl chloride in the reaction mixture reacts further to give dibenzoylated products. The latter half of the reaction in Figure II is quite similar to the reaction with A:B:T = 1:4:4 (Figure I). This result apparently indicates the role of triethylamine in the dibenzoylation.

Benzoylation of Monobenzoylaminopyridine.

Q. E. Thompson (6) has reported that benzamide as a primary amide was reacted with benzoyl chloride in the presence of pyridine to give tribenzamide, while dibenzamide, which was a supposed intermediate in the dibenzoylation of benzamide, could not be converted to tribenzamide under similar conditions. He also pointed out that the primary amine as a starting material could not be dibenzoylated under the same conditions. In the subsequent studies by D. Davidson and H. Skovronek (7), a one step dibenzoylation mechanism of primary amides has been proposed. On the other hand, several workers (2) (3) have prepared α-dibenzoylaminopyridine from α-aminopyridine, but it has not been clarified if the dibenzoylation occurs *via* the monobenzoylated intermediate.

Both Figure I and II, however, suggest that the dibenzoylation of aminopyridine proceeds *via* monobenzoylaminopyridine, though only α-aminopyridine is too reactive to detect the intermediate. Benzoylation of monobenzoylaminopyridine (M) with benzoyl chloride (B) was then carried out in the presence of triethylamine (T) with the molar ratio of M:B:T = 1:2:2 in acetonitrile at 0°. The results (Figure III) show that monobenzoylaminopyridine can be further benzoylated with a different reactivity of $\alpha > \beta > \gamma$.

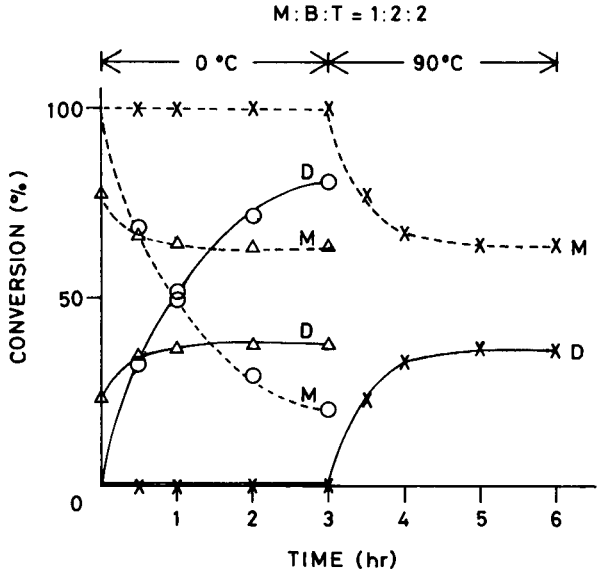

Figure III. Benzoylation of monobenzoylaminopyridine. Letters, B, T, M, D, α, β and γ are same as those in Figure I. Reaction condition; M: 1.0 mmole, solvent: acetonitrile (50 ml.).

From all of the above results, it is concluded that any of three isomeric aminopyridines can be readily converted to the corresponding dibenzoylaminopyridine *via* the monobenzoylated intermediate by treatment with an excess of benzoyl chloride in the presence of an excess of triethylamine. α-Aminopyridine is especially reactive, thus the monobenzoylated intermediate can hardly be detected.

EXPERIMENTAL

Melting points, yields and elemental analyses of dibenzoylaminopyridines and *N*-pyridylphthalimides are summarized in Table I.

Dibenzoylaminopyridines (D-α ~ γ).

A solution of benzoyl chloride (6.0 g., 42.8 mmoles) in chloroform (30 ml.) was added dropwise to a solution of aminopyridine (1.0 g., 10.6 mmoles) and triethylamine (4.0 g., 39.6 mmoles) in chloroform (40 ml.) at 0°. Then, after heating under reflux for 5 hours, the mixture was evaporated to dryness under reduced pressure. The residue was washed with hexane and extracted with acetone. The extract was again evaporated to give a solid, which was passed through a silica gel column with hexane, benzene and acetone as eluents, in that order. The acetone fraction was evaporated to dryness under reduced pressure and then recrystallized repeatedly from hexane or hexane-benzene, yielding 3.0 g., 2.7 g. and 2.8 g. of α-, β- and γ-dibenzoylaminopyridine, respectively; ir (potassium bromide): D-α: 1680 (s), 1595 (m), 1585 (s), 1470 (m), 1445 (s), 1430 (s), 1300 (s), 1290 (s), 1260 (s), 1235 (s), 1170 (m), 1130 (s), 1070 (m), 1025 (m), 990 (m), 935 (m), 855 (s), 800 (s), 790 (s), 745 (m), 740 (m), 710 (s), 700 (s), 690 (m), 650 (s) cm^{-1}; D-β: 1705 (m), 1660 (s), 1600 (w), 1580 (w), 1480 (w), 1420 (m), 1340 (s), 1245 (m), 1230 (s), 1140 (s), 1025 (w), 895 (m), 850 (m), 805 (w), 790 (m), 725 (m), 700 (m), 690 (m), 660 (m) cm^{-1}; D-γ: 1690 (s), 1580 (s), 1560 (m), 1490 (w), 1445 (w), 1410 (w), 1335 (w), 1290 (s), 1260 (s), 1235 (s), 1180 (m), 1120 (s), 1070 (m), 1025 (m), 1000 (w), 940 (w), 860 (w), 850 (m), 810 (s), 795 (s), 740 (s), 715 (s), 705 (s), 690 (m), 660 (s), 640 (m), 530 (w) cm^{-1}; ms: (m/e) 302 M^+.

N-Pyridylphthalimides (P-α ~ γ).

A solution of phthaloyl dichloride (0.55 g., 2.7 mmoles) in chloroform (10 ml.) was added dropwise to a solution of aminopyridine (0.25 g., 2.7 mmoles) and triethylamine (1.0 g., 9.9 mmoles) in chloroform (30 ml.). Then, after heating under reflux for 10 hours, the mixture was evaporated to dryness under reduced pressure. The residue was washed with hexane and extracted with acetone. The extract was evaporated to dryness under reduced pressure and then recrystallized repeatedly from ethanol, yielding 0.36 g., 0.30 g. and 0.43 g. of *N*-(α-, β- and γ-pyridyl)-phthalimide, respectively; ir (potassium bromide): P-α: 1790 (m), 1750 (s), 1720 (s), 1590 (s), 1470 (s), 1440 (s), 1415 (w), 1385 (s), 1140 (m), 1115 (s), 1085 (m), 995 (m), 900 (w), 880 (m), 860 (m), 800 (w), 780 (s), 750 (w), 720 (s), 700 (m), 645 (m), 530 (m), 515 (w) cm^{-1}; P-β: 1780 (w), 1735 (m), 1705 (s), 1480 (m), 1425 (s), 1385 (s), 1225 (w), 1110 (m), 1090 (w), 875 (m), 805 (w), 800 (w), 720 (s), 705 (m), 640 (w), 530 (w) cm^{-1}; P-γ: 1775 (w), 1740 (m), 1710 (s), 1580 (s), 1500 (w), 1455 (w), 1420 (w), 1365 (s), 1220 (m), 1100 (m), 1060 (m), 880 (m), 820 (w), 805 (m), 720 (m), 610 (m), 525 (m) cm^{-1}.

Measurement of the Conversion Rate by Hplc.

The authentic monobenzoylaminopyridines (M-α ~ γ) were prepared by partial hydrolysis of α-dibenzoylaminopyridine or controlled benzoylation of β- and γ-aminopyridines, respectively. These products were identified by comparison with those in the literature (2) (8).

The conversion rate in the case of the initial molar ratio of reactants with A:B:T = 1:4:4 was measured by high pressure liquid chromatography as follows. Other cases were carried out in a similar way.

Aminopyridine (94 mg., 1.0 mmole), triethylamine (0.56 ml., 4.0 mmoles) and *p*-dichlorobenzene (3.0 g., 20.4 mmoles) as an internal standard were weighed accurately and dissolved in chloroform (10 ml.) in a 30 ml. flask. Immediately after benzoyl chloride (0.47 ml., 4.0 mmoles) was added to the solution, the flask was dipped into an oil bath heated at 70°. At a certain interval after the dipping, each 0.1 ml. portion of the reaction mixture was sampled, poured into 0.7 ml. of 97% moist acetonitrile, and then subjected to high pressure liquid chromatography to determine

quantitatively the benzoylated products.

The conditions of hplc are: column, 3 mmϕ x 300 mm.; stationary phase, LS110-B-P10(a) or LS-111-P15(b) (Toyo Soda Co.); mobile phase, methanol/water = 97/3 (vol.); flow rate, 0.7 ml./minute; pressure, 40 kg./cm^2.; detector, UV (254 nm.).

Product (Stationary Phase)		Retention Time (Minutes)	Molar Sensitivity Ratio (Standard) (Product/Internal Standard)
α (LS-111)	M-	17.2	0.9706 (acetophenone)
	D-	24.4	0.5027 (acetophenone)
β (LS-110)	M-	6.4	340.1 (*p*-dichlorobenzene)
	D-	10.4	120.8 (*p*-dichlorobenzene)
γ (LS-110)	M-	7.2	392.8 (*p*-dichlorobenzene)
	D-	12.0	155.6 (*p*-dichlorobenzene)

(a) Styrene-divinylbenzene porous copolymer gel, particle diameter, 10 μm. (b) Styrene-divinylbenzene porous copolymer gel, particle diameter, 15 μm.

REFERENCES AND NOTES

(1) T. Suzuki, N. Katou and K. Mitsuhashi, *J. Heterocyclic Chem.*, **15**, 1451 (1978).

(2) E. H. Huntress and H. C. Walter, *J. Org. Chem.*, **13**, 735 (1948).

(3) P. A. Lyon and C. B. Reese, *J. Chem. Soc., Perkin Trans. I*, 2645 (1974).

(4) G. Crippa, M. Long and E. de Matini, *Gazz. Chim. Ital.*, **64**, 83 (1934).

(5) E. Koenigs and H. Greiner, *Ber.*, **64B**, 1049 (1931).

(6) Q. E. Thompson, *J. Am. Chem. Soc.*, **73**, 5841 (1951).

(7) D. Davidson and H. Skovronek, *ibid.*, **80**, 376 (1958).

(8) P. Grammaticakis, *Bull. Soc. Chim. France*, 480 (1959).