Acylation of Heteroaromatic Amines (I). Perbenzoylation of Diaminopyridazines.

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Some diaminopyridazines such as 4,7-diaminoimidazo[4,5-*d*]pyridazine, 1-methyl-4,7-diaminoimidazo[4,5-*d*]pyridazine, 5,8-diaminopyrazino[2,3-*d*]pyridazine, 2,3-dimethyl-5,8-diaminopyrazino[2,3-*d*]pyridazine and 1,4-diaminophthalazine, all of which were prepared by the reaction of hydrazine with the respective *vic*-dicyanide as starting material, were reacted with benzoyl chloride in the presence of triethylamine, giving novel perbenzoylated derivatives in good yield. A dibenzoylation mechanism of the amino group has been proposed.

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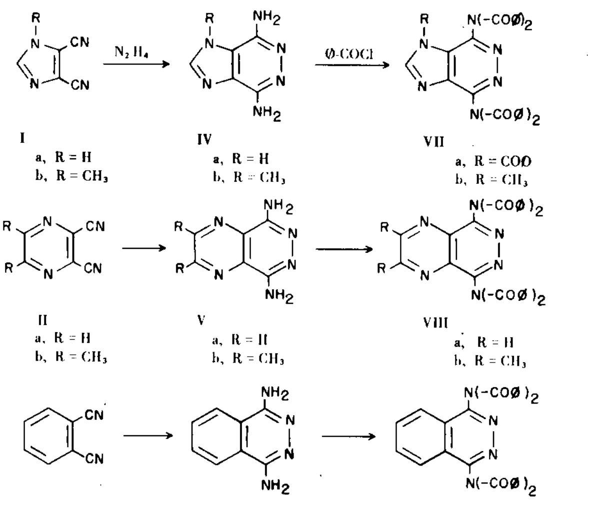
Derivatives of heteroaromatic amines, especially their primary amides, have been widely studied for pharmaceutical application and macromolecular development, whereas their secondary amides have been little reported.

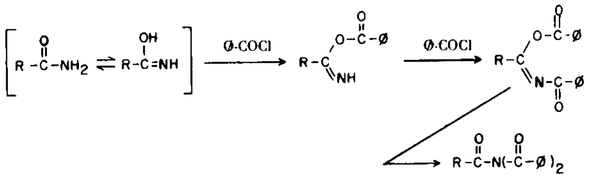
It is well known that aromatic primary amines are readily monobenzoylated in many ways, but no detectable dibenzoylation of these amines occurs. E. H. Huntress (1), however, has prepared 2-dibenzoylaminopyridine by the Schotten-Baumann benzoylation of 2-aminopyridine. Apparently, little work concerning dibenzoylation of heteroaromatic amines has been reported.

In the present work, 4,7-diaminoimidazo[4,5-*d*]pyridazine, 1-methyl-4,7-diaminoimidazo[4,5-*d*]pyridazine, 5,8-diaminopyrazino[2,3-*d*]pyridazine, 2,3-dimethyl-5,8-diaminopyrazino[2,3-*d*]pyridazine and 1,4-diaminophthalazine, all of which were prepared by the reaction of hydrazine with the respective *vic*-dicyanide as starting material, were reacted with benzoyl chloride in the presence of triethylamine, giving novel perbenzoylated derivatives in good yield.

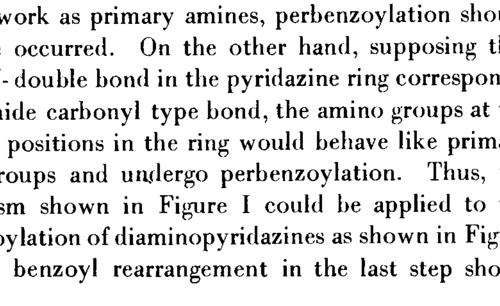
SCHEME I



Q. E. Thompson (2) 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 co-workers (3), a one step dibenzoylation mechanism of primary amides has been proposed as shown in Figure I.



Consequently, regarding diaminopyridazines in the present work as primary amines, perbenzoylation should not have occurred. On the other hand, supposing that the C=N- double bond in the pyridazine ring corresponds to an amide carbonyl type bond, the amino groups at the 3 and 6 positions in the ring would behave like primary amide groups and undergo perbenzoylation. Thus, the mechanism shown in Figure I could be applied to the perbenzoylation of diaminopyridazines as shown in Figure II. The benzoyl rearrangement in the last step shown in Figure II seems to be likely owing to the aromatic stability of the pyridazine ring.

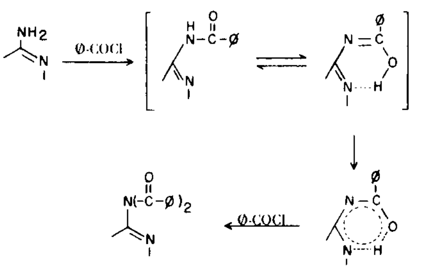


Such a one step dibenzoylation of amino groups is presumably characteristic of an amino group attached to the carbon atom α to the unsaturated nitrogen in the pyridazine ring. An alternative mechanism is proposed as shown in Figure III.

Table I

Perbenzoylated Diaminopyridazines

Product	M.p. °C	Yield %	Formula	Analyses Calcd. C	 H	 N	 Found C	 H	 N
VIIa	259-262 dec.	63	$C_{40}H_{26}N_6O_5$	71.64	3.88	12.54	71.57	3.77	12.38
VIIb	250 dec.	68	$C_{34}H_{24}N_6O_4$	70.34	4.14	14.48	70.08	4.02	14.31
VIIIa	260-261 dec.	76	$C_{34}H_{22}N_6O_4$	70.59	3.81	14.53	70.60	3.53	14.27
VIIIb	230-231 dec.	72	$C_{36}H_{26}N_6O_4$	71.29	4.29	13.86	71.01	4.07	13.74
IX	255-257 dec.	74	$C_{36}H_{24}N_4O_4$	75.00	4.17	9.72	75.20	4.24	9.62



EXPERIMENTAL

All ir spectra were measured in potassium bromide disks. Melting points of diaminopyridazines (IV-VI) were determined by means of a differential thermal analysis, while those of the benzoylated derivatives (VII-IX) were observed in a capillary and uncorrected.

Preparation of Diaminopyridazines.

Each diaminopyridazine was prepared by the reaction of the respective starting *vic*-dicyanide with hydrazine, according to Castle's method (4).

4,7-Diaminoimidazo[4,5-*d*]pyridazine (IVa).

Acetic acid (2 ml., 35.6 mmoles) was added to a solution of 4,5-dicyanoimidazole (Ia) (3 g., 25.4 mmoles) in 80% hydrazine monohydrate (30 ml., 494 mmoles) at room temperature. After heating the mixture at 70-80° for 3.5 hours, the resulting pale yellow precipitate was collected on a filter. Repeated recrystallization from methanol yielded 0.9 g. (21%) of (IVa) monohydrate as pale yellow needles, m.p. 327-330° dec. (lit. (5) 314-316°); ir: 1675 (s), 1630 (m), 1555 (m), 1485 (m), 1435 (s), 1280 (m), 1195 (m), 1065 (m), 805 (m) cm^{-1}; ms: (m/e) 150 M$^+$ (-H$_2$O).

Anal. Calcd. for $C_5H_6N_6(H_2O)$: C, 35.71; H, 4.76; N, 50.00. Found: C, 35.64; H, 4.53; N, 50.24.

Compounds IVb, Va, Vb and VI were prepared by a similar procedure.

1-Methyl-4,7-diaminoimidazo[4,5-*d*]pyridazine (IVb).

Pale yellow needles of IVb were obtained by recrystallization from methanol in a yield of 1.1 g. (44%) from 2 g. of Ib, m.p. 305-307° dec.; ir: 1625 (s), 1585 (s), 1505 (w), 1450 (s), 1350 (m), 1340 (m), 1285 (w), 1230 (m), 1160 (m), 1070 (m), 1035 (m), 1000 (m), 820 (m), 730 (s) cm^{-1}; ms: (m/e) 164 M$^+$.

Anal. Calcd. for $C_6H_8N_6$: C, 43.90; H, 4.88; N, 51.22. Found: C, 44.08; H, 4.78; N, 50.99.

5,8-Diaminopyrazino[2,3-*d*]pyridazine (Va).

Orange needles of Va were obtained by recrystallization from water in a yield of 0.7 g. (56%) from 1 g. of IIa, m.p. 343-346° dec. (lit. (6) 233-234° dec.); ir: 1605 (s), 1465 (s), 1365 (m), 1150 (m), 1050 (m), 885 (m), 690 (s) cm^{-1}; ms: (m/e) 162 M$^+$.

Anal. Calcd. for $C_6H_6N_6$: C, 44.44; H, 3.70; N, 51.85. Found: C, 44.38; H, 3.82; N, 51.64.

2,3-Dimethyl-5,8-diaminopyrazino[2,3-*d*]pyridazine (Vb).

Orange needles of Vb were obtained by recrystallization from water in a yield of 0.7 g. (58%) from 1 g. of IIb, m.p. 329-333° dec.; ir: 1605 (s), 1475 (s), 1390 (m), 1355 (m), 1205 (m), 990 (w) cm^{-1}; ms: (m/e) 190 M$^+$.

Anal. Calcd. for $C_8H_{10}N_6$: C, 50.53; H, 5.26; N, 44.21. Found: C, 50.30; H, 5.19; N, 43.99.

1,4-Diaminophthalazine (VI).

Yellow needles of VI monohydrate were obtained by recrystallization from water in a yield of 0.7 g. (34%) from 1.5 g. of III, m.p. 252-255° dec. (lit. (7) 255° dec.); ir: 1635 (s), 1550 (w), 1495 (s), 1440 (s), 1355 (m), 1260 (w), 1160 (m), 1000 (m), 780 (m), 680 (m) cm^{-1}; ms: (m/e) 160 M$^+$ (-H$_2$O).

Benzoylation of Diaminopyridazines.

Melting points, yields and elemental analyses of these products are summarized in Table I.

1-Benzoyl-4,7-di(dibenzoylamino)imidazo[4,5-*d*]pyridazine (VIIa).

A solution of benzoyl chloride (5.6 ml., 47.8 mmoles) in chloroform (10 ml.) was added dropwise to a mixture containing 4,7-diaminoimidazo[4,5-*d*]pyridazine (IVa) monohydrate (1 g., 6.3 mmoles) and triethylamine (6.6 ml., 45.7 mmoles) in chloroform (30 ml.) at room temperature. After refluxing for 9 hours, the mixture was evaporated to dryness under reduced pressure. The residue was washed with *n*-hexane, water and hot methanol in that order, and then recrystallized repeatedly from acetone, yielding 2.5 g. of VIIa as white needles; ir: 1710 (s), 1690 (s), 1600 (m), 1585 (m), 1485 (w), 1450 (m), 1425 (m), 1400 (m), 1290 (s), 1260 (s), 1240 (s), 1200 (m), 1175 (m), 1130 (m), 1070 (w), 980 (w), 905 (m), 880 (m), 855 (w), 780 (m), 725 (m), 695 (m) cm^{-1}.

Compounds VIIb, VIIIa, VIIIb and IX were prepared by a similar procedure. The molar ratio of benzoyl chloride and triethylamine to the corresponding diaminopyridazine in the initial reaction mixture is given for each compound shown below as B:T:A.

1-Methyl-4,7-di(dibenzoylamino)imidazo[4,5-*d*]pyridazine (VIIb).

White needles of VIIb were obtained by recrystallization from methanol in a yield of 2.4 g. from 1 g. of IVb, B:T:A = 6.0:5.8:1; ir: 1700 (s), 1600 (m), 1450 (m), 1400 (s), 1315 (s), 1250 (s), 1180 (m), 1140 (m), 785 (m), 735 (m), 710 (m) cm^{-1}.

5,8-Bis(dibenzoylamino)pyrazino[2,3-*d*]pyridazine (VIIIa).

White needles of VIIIa were obtained by recrystallization from benzene in a yield of 2.7 g. from 1 g. of Va, B:T:A = 5.9:5.8:1; ir: 1700 (s), 1600 (m), 1450 (m), 1415 (m), 1390 (s), 1275 (s), 1245 (s), 1180 (m), 1130 (m), 910 (m), 780 (m), 690 (m) cm^{-1}.

2,3-Dimethyl-5,8-bis(dibenzoylamino)pyrazino[2,3-*d*]pyridazine (VIIIb).

White needles of VIIIb were obtained by recrystallization from methanol in a yield of 2.3 g. from 1 g. of Vb, B:T:A = 4.8:4.2:1; ir: 1700 (s), 1600 (m), 1445 (m), 1405 (s), 1385 (m), 1370 (m), 1270 (s), 1240 (s), 1130 (m), 900 (w), 850 (w), 780 (m), 725 (m), 700 (s) cm^{-1}-

1,4-Bis(dibenzoylamino)phthalazine (IX).

White needles of IX were obtained by recrystallization from acetone in a yield of 2.4 g. from 1 g. of VI monohydrate, B:T:A = 6.8:9.9:1; ir: 1705 (s), 1605 (m), 1455 (m), 1400 (m), 1370 (s), 1280 (s), 1255 (s), 1180 (m), 1120 (m), 775 (m), 735 (m), 700 (m) cm^{-1}.

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