HETEROCYCLES, Vol. 24, No. 8, 1986

NOVEL SYNTHESIS OF PYRIDOPYRIMIDINE DIONES[1]

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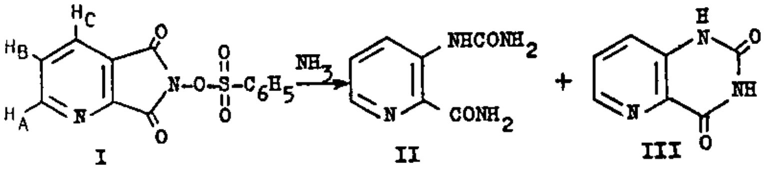
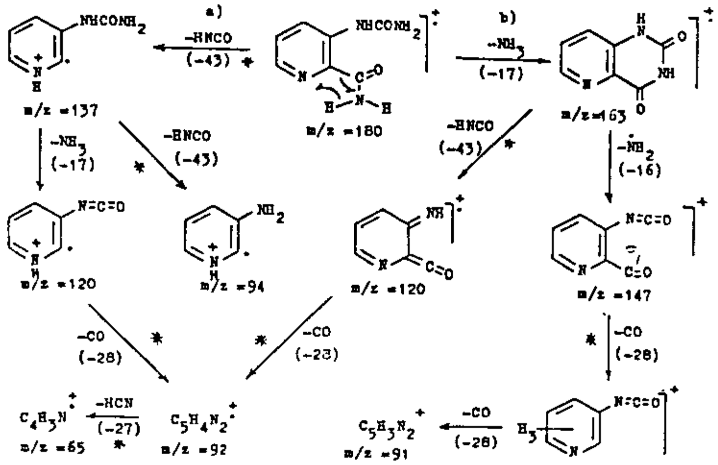
Abstract — N-(Phenylsulphonyloxy)quinolinimide (I) reacts with different nucleophiles to give II-VIII. It was proved that the nucleophilic attack occurs at the more electro-positive carbonyl group to give only one product in good yields.

Pyridopyrimidine derivatives possessing long lasting diuretic and selective natrivertic activities[2] and some of them having analgesic antiinflammatory and central nervous system depressing activities[3]. In this work, we have synthesized unreported pyrido[3,2-d]pyrimidine-2,4-diones through the reaction of N-(phenylsulphonyloxy)quinolinimide (I) with different nucleophiles.

Ammonolysis of N-(phenylsulphonyloxy)quinolinimide(I) with dry ammonia at room temperature gives a mixture of 2-carbamoyl-3-pyridylurea(II) and 1H,3H-pyrido-[3,2-d]pyrimidine-2,4-dione(III). Fusion of II gives III with evolution of ammonia in 98% yield.

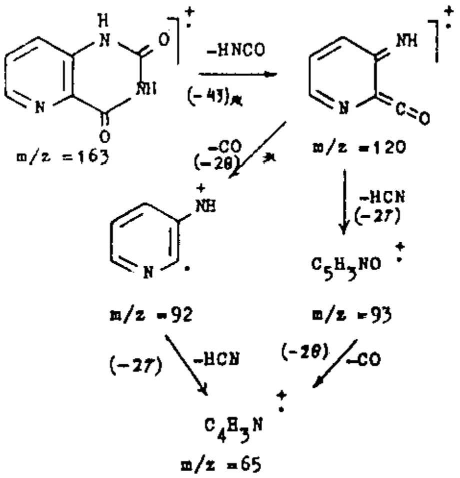


Structure of II and III was confirmed on the basis of elemental analyses and spectroscopic data. The ^1H nmr spectrum of II (DMSO, 250 MHz) showed the following signals: 6.67 (NH_2 in the 3-position, 2H, br s), 7.45-7.50 (H_B, 1H, d of d), 7.8 and 8.34 (NH_2 in the 2-position[4], 2H, two br s), 8.13-8.16 (H_A, 1H, d of d), 8.79-8.83 (H_C, 1H, d of d) and 10.9 (NH, 1H, s). Mass spectrum of II showed molecular ion at m/z 180 and the latter undergoes the fragmentation pathways[5] (a and b) as shown in Scheme 1.



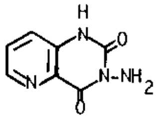
Scheme 1

Mass spectrum of III showed molecular ion at m/z 163 which undergoes fragmentation[5] as shown in Scheme 2.



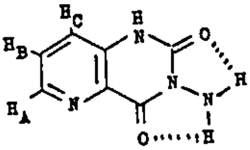
Scheme 2

Compound I reacts vigorously with hydrazine hydrate in dry benzene at room temperature to give 3-aminopyrido[3,2-d]pyrimidine-2,4-dione(IV).

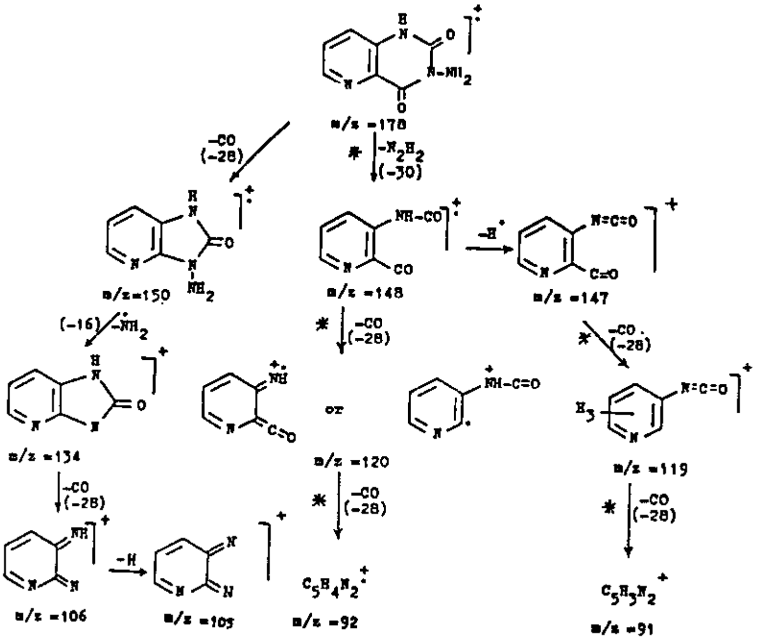


IV

The ^1H nmr (DMSO, 250 MHz) for IV showed the following signals: 5.55, 5.57 (d, 2H, NH_2), 7.59-7.68 (m, 2H, H_B + H_C), 8.51 (d of d, 1H, H_A), 11.69 (br, 1H, NH). The splitting of the NH_2 group into doublet is propably due to the intramolecular hydrogen bonding between the NH_2 protons and the two carbonyl oxygen which are not equivalent. These hydrogens are magnetically nonequivalent and they appear at different chemical shifts.

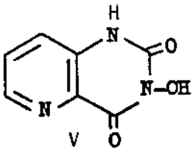


The mass spectrum of IV showed molecular ion at m/z 178 and the latter undergoes the fragmentations shown in Scheme 3.



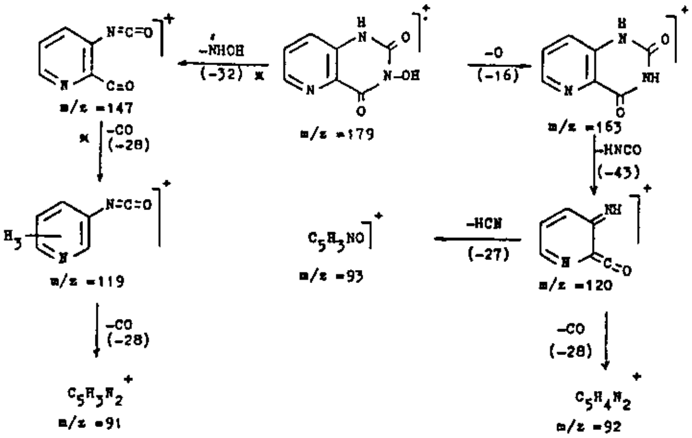
Scheme 3

When hydroxylamine hydrochloride was added to I in dry pyridine it gives 3-hydroxypyrido[3,2-d]pyrimidine-2,4(1H)-dione (V).



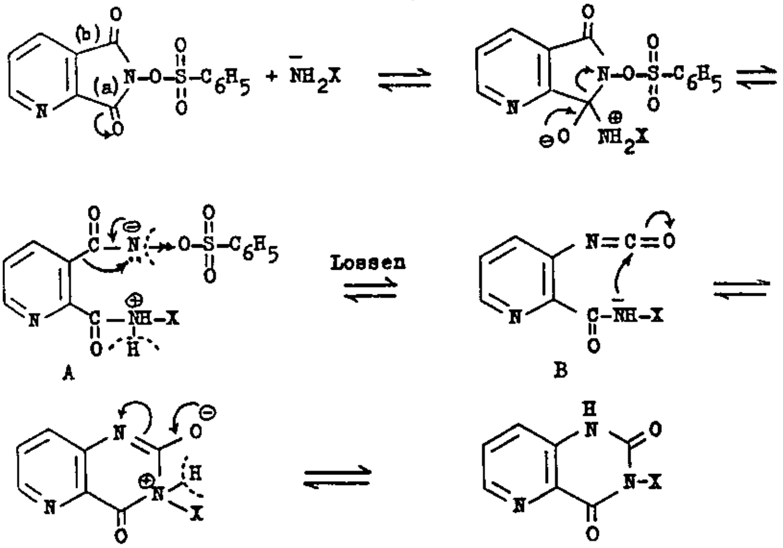
V

The structure of V was elucidated by elemental analysis as well as spectroscopic data. The ^{1}H nmr (DMSO, 60 MHz) showed signals at: 8.63-7.28 (Ar-H), 10.7 (br, 1H, OH) and 12.06 (br, 1H, NH). The mass spectrum showed molecular ion at m/z 179 which undergoes the fragmentation as shown in Scheme 4.



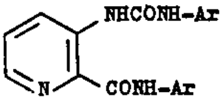
Scheme 4

The reaction of I with ammonia, hydrazine hydrate and hydroxylamine hydrochloride to give III, IV and V respectively propably takes place in the following steps: (Scheme 5)- (i) Nucleophilic attack at the carbonyl carbon (a) to give A. (ii) Lossen rearrangement of A to give the intermediate isocyanate B. (iii) Cyclization of B to give the products.



Scheme 5

Treatment of I with aromatic amines namely aniline, p-toluidine and p-anisidine in benzene at room temperature afforded sym-N-2-(arylcarbamoyl)-3-pyridyl-N'-arylureas (VIa-c).

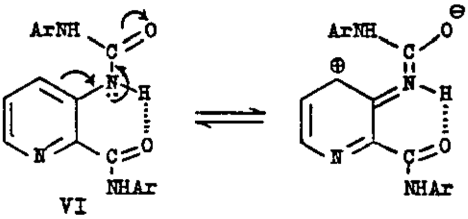


VI

a, Ar = C_6H_5; b, Ar = $C_6H_4CH_3$(p-); c, Ar = $C_6H_4OCH_3$(p-).

The structure of VIa-c was confirmed on the basis of elemental analyses as well as spectroscopic data. The ^1H nmr of VIa (DMSO, 60 MHz) showed signals at: 6.83-7.78 (Ar-H + H_B, 11H, m), 8.13 (H_B, 1H, d of d), 8.70 (H_C, 1H, d of d) and 9.72, 10.55, 10.72 (3 NH). Compound VIb (DMSO, 60 MHz) showed signals at: 6.88-7.72 (Ar-H + H_B, 9H, m), 8.13 (H_B, 1H, d of d), 8.73 (H_C, 1H, d of d), 9.63, 10.52, 10.77 (3NH) and 2.23, 2.27 (6H, 2 CH_3,2s). Compound VIc (DMSO, 250 MHz) showed signals at: 6.85-6.89, 6.93-6.97 and (7.41-7.44, 7.74-7.77), 8H, 2 AA'BB', 7.58 (H_B, 1H d of d), 8.29 (H_A, 1H d of d), 8.87 (H_C, 1H d of d), 9.67, 10.63, 10.94 (3 NH, 3s) and 3.72, 3.76 (2 OCH_3, 6H, 2s).

It should be noted in the ^1H nmr spectrum of the compound VIa-c that H_C is the most deshielded proton which can be explained by the following resonance structures.

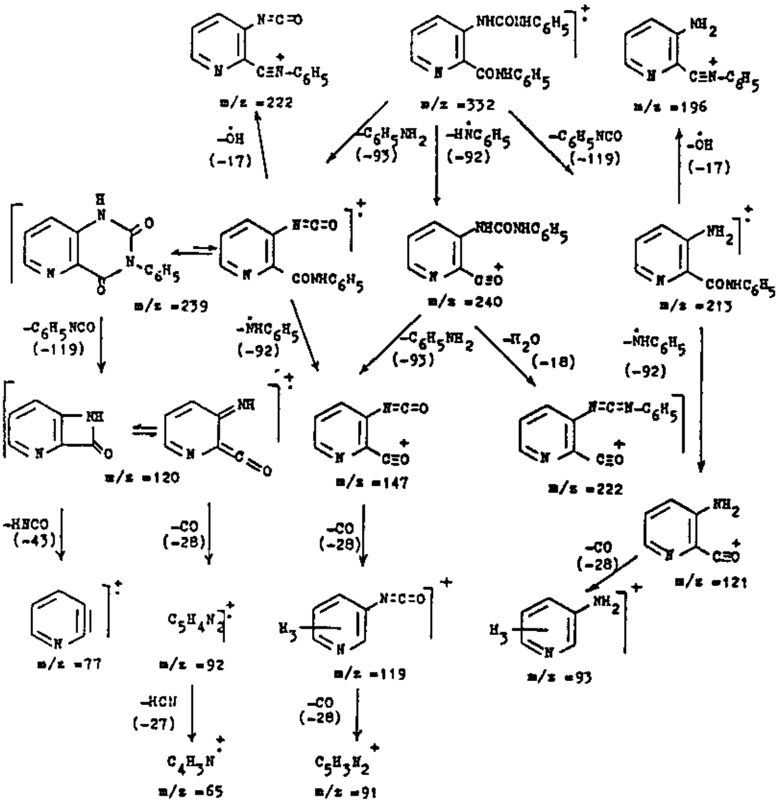


VI

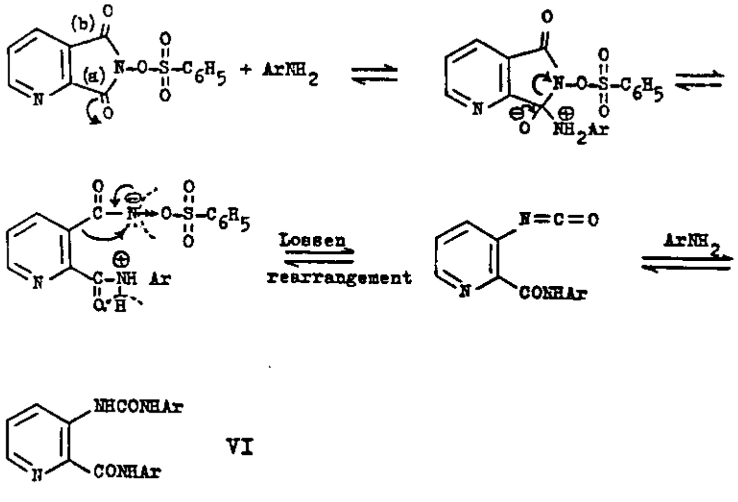
It should also be noted that, the secondary amino group in the 3-position can engage in hydrogen bonding with the carbonyl group in the 2-position, and so restricts the confirmational possibilities for the carbonyl urea, therefore its an isotropic effect should be taken into consideration.

Mass spectra of VIa-c showed molecular ions at m/z 332, 360 and 392 respectively. These ions undergo the fragmentation as shown in Scheme 6.

The formation of sym-N-2-(arylcarbamoyl)—3-pyridyl-N'-arylureas VIa-c by the reaction of N-(phenylsulphonyloxy)quinolinimide I with aromatic amines may explain by the mechanism shown in Scheme 7.



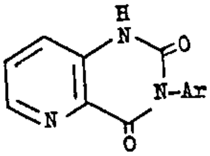
Scheme 6



Scheme 7

Fusion of VIa-c above its melting point (by 10°C), under reduced pressure, it gives

3-arylpyrido[3,2-d]pyrimidine-2,4(1H)-dione VIIa-c.

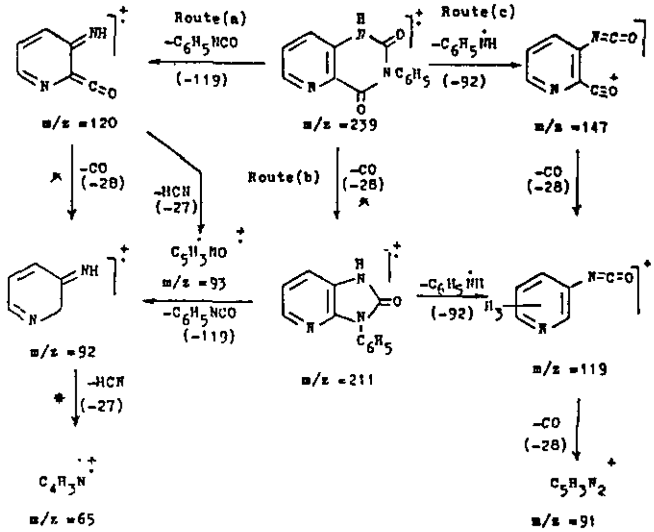


VII

a) Ar = C_6H_5; b, Ar = $C_6H_4CH_3$(p); C, Ar = $C_6H_4OCH_3$(p)

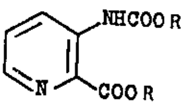
Structure of VIIa-c was confirmed by elemental analyses and spectroscopic data. The ^{1}H nmr of VIIa (DMSO, 250 MHz) showed signals at: 7.30-7.52 (Ar-H, 5H, m), 7.62-7.71 (H_C + H_B, 2H, m), 8.50 (H_A, 1H d of d) and 11.49 (NH, 1H, s). For VIIc (DMSO, 250 MHz) showed signals at: 7.01-7.06 and 7.21-7.26 (Ar-H, 4H and AA'BB'), 7.62 (H_C, 1H d of d), 7.69 (H_B, 1H, d of d), 8.50 (H_A, 1H, d of d), 11.57 (NH, 1H, s) and 3.81 (OCH_3, 3H, s).

Mass spectra of VIIa-c showed molecular ions at m/z 239, 253 and 269 respectively. These ions undergo fragmentation as shown in Scheme 8.



Scheme 8

When I was boiled in absolute ethanol and/or absolute methanol in the presence of pyridine as a catalyst it give ethyl-(3-ethoxycarbonylamino)-2-pyridine carboxylate and methyl-(3-methoxycarbonylamino)-2-pyridine carboxylate (VIIIa-b) respectively.

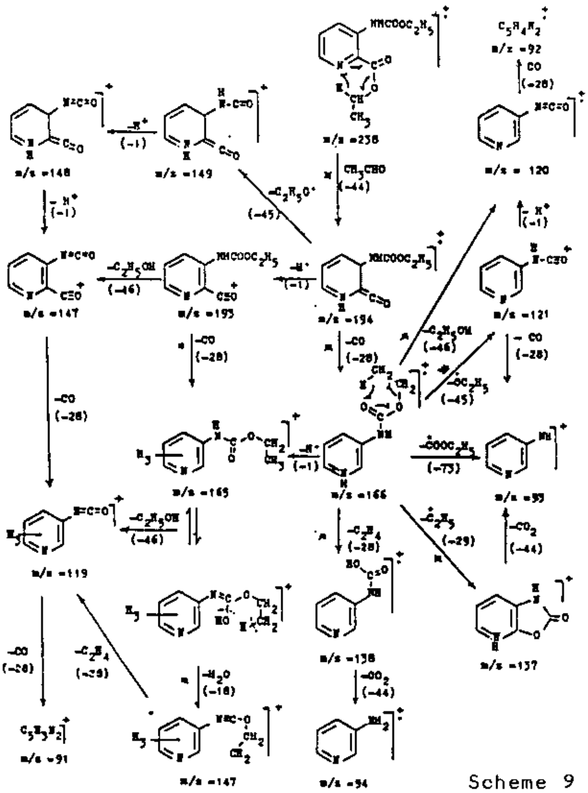


VIII

a, R = C_2H_5; b, R=CH_3

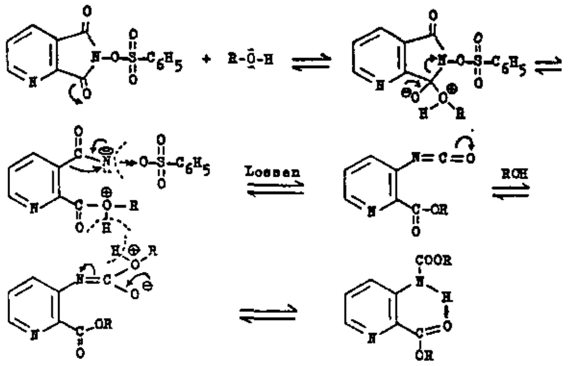
The structure of VIIIa,b was confirmed on the basis of elemental analyses as well as spectroscopic data.

The ^1H nmr[4,6-9] for VIIIa ($CDCl_3$, 250 MHz) showed signals at: 1.34 (CH_3 in the 3-position, 3H, t), 1.47 (CH_3 in the 2-position, 3H, t), 4.25 (CH_2 in the 3-position, 2H, q), 4.51 (CH_2 in the 2-position, 2H, q), 7.46 (H_B, 1H, d of d of d), 8.39 (H_A, 1H, d of d), 8.88 (H_C, 1H, d of d), 10.44 (NH, 1H, br s). Mass spectrum[10-15] showed the presence of molecular ion at m/z 238. The major fragmentation pathways are illustrated in Scheme 9. The ^1H nmr ($CDCl_3$, 250 MHz) for VIIIb showed the following signals: 3.81 (CH_3 in the 3-position, 3H, s), 4.02 (CH_3 in the 2-position, 3H, s), 7.48 (H_B, 1H, d of d of d), 8.38 (H_A, 1H, d of d), 8.86 (H_C, 1H, d of d), 10.44 (NH, 1H, s). Its mass spectrum revealed molecular ion at m/z 210.



Scheme 9

The reaction of alcohols namely ethanol and methanol with N-(phenylsulphonyloxy)-quinolinimide (I) probably takes place according to the following Scheme:



Scheme 10

On the other hand, 3-arylpyrido[3,2-d]pyrimidine-2,4(1H)-diones VIIa-c were prepared by an alternative route via heating VIIIa with aromatic amines at 200-220°C. The products obtained by this method were identical is all aspects (mp, mmp, ir, nmr & ms) with those prepared by the previous method.

EXPERIMENTAL

All mp's are not corrected. The ir spectra were carried out on a Acculab. 1,Beckman using KBr wafer technique. ^{1}H nmr (60 MHz) were measured on T 60, Varian (measuring temperature T = 35 ± 1 °C) and ^{1}H nmr (250 MHz) were measured on PTF-NMR Spectrometer WM 250 (measuring temperature T = 23 ± 1°C). Low resolution mass spectra was recorded on monofocusing Varian MAT CH-5 mass spectrophotometer at ionization energy 70 eV and using direct insertion probe. High resolution and metastable ms were recorded on a Varian 311 A, double focusing instrument with reversed geometry at 70 eV.

Action of Benzenesulphonyl Chloride on N-Hydroxyquinolinimide. Formation of I.

Benzenesulphonyl chloride (470 mg, 260 mmol) was added to a solution of N-hydroxyquinolinimide[16] (400 mg, 250 mmol) in pyridine (4 ml). The reaction mixture was stirred for 15 min. The solid formed was removed by filteration, washed with 5% sodium bicarbonate solution, then dired and crystallized from toluene to give *(556 mg, 1.83 mmol , yield 75%) of I, mp 191-192°C* as colourless needles. Anal. Calcd. for $C_{13}H_8N_2O_5$: C, 51.27; H, 2.65; N, 9.20. Found: C, 51.29; H, 2.63; N,9.21. The ir showed a doublet at 1790 and 1730 cm^{-1} (νC=0) as expected for coupling carbonyl band of cyclic imides[17,18], and at 1380, 1180 cm^{-1} for (SO_2-0-). ^{1}H nmr

(DMSO, 60 MHz) showed signals at:7.91 (Ar-H + H_B, 6H, m), 8.3 (H_C, 1H, d of d) and 8.89 (H_A, 1H, d of d). Mass spectrum showed the following m/z (rel. int %): 304 M^+ (10), 148(5), 143(6), 142(7), 141(100), 105(17), 78(7), 77(89), 51(10) and 50(7).

Action of Ammonia on N-(Phenylsulphonyloxy)quinolinimide I. Formation of II and III.

Dry ammonia gas was allowed to pass through a suspension of 400 mg (1.31 mmol) of I in dry benzene (25 ml) for 1 h. The solvent was removed under reduced pressure, and the solid formed was washed with ethanol. By means of column chromatography (silica gel, 20 cm height, 3 cm diameter), (150 mg, 0.83 mmol) of 2-carbamoyl-3-pyridylurea (II) and (50 mg, 0.3 mmol) of pyrido[3,2-d]pyrimidine-2,4(1H , 3H)-dione (III) were separated as colurless solids using ethylacetate as an eleuent. Compound II, mp 220-221°C dec , yield 63°%. Anal. Calcd. for $C_7H_8H_4O_2$: C, 46.66; H, 4.47; N, 31.10. Found: 46.51; H, 4.53; N, 30.77. Ir spectrum revealed pair of bands at 3380 and 3190 cm^{-1} characteristic for primary amides[19] and at 1685, 1660 cm^{-1} for C=O's. Ms showed m/z (rel. int %): 180 M^+(28), 163(16), 147(5), 137(100), 136(8), 120(29), 119(12), 94(17), 93(17), 92(34), 91(6), 67(11), 66(11), 65(7), 64(4). Compound III, mp 340-345°C, yield 23%. Anal. Calcd. for $C_7H_5N_3O_2$: C, 51.53; H, 3.09; N, 25.76. Found: C, 50.93; H, 3.50; N, 25.72. The ir showed many bands for NH in the region 3180-2730 cm^{-1}, and for C=O at 1720 and 1690 cm^{-1}. The ms showed m/z (rel. int. %): 163 M^+ (98), 120 (53), 93(7), 92(100), 91(7), 66(12), 65(35), 64(16), 58(14).

Fusion of (100 mg, 0.55 0.55 mmol) of 2-carbamoyl-3-pyridylurea (II) at 250°C for 15 min , it gives (88.7 mg, 0.54 mmol , yield 98%) of pyrido[3,2-d]pyrimidine-2,4-(1H ,3H)-dione (III).

Action of Hydrazine Hydrate on I. Formation of IV.

Hydrazine hydrate 460 mg (9.2 mmol) was added to a suspension of N-(phenylsulphonyloxy)quinolinimide (I) (700 mg, 2.3 mmol) in dry benzene. The reaction mixture was stirred for 1 h and the solvent was removed under vacuo. The solid formed was then washed with ethanol and crystallized from acetic acid to give 279 mg (1.57 mmol , 68%) of 3-aminopyrido[3,2-d]pyrimidine-2,4(1H)-dione (IV) as colourless solid, mp 320-325°C. Anal. Calcd. for $C_7H_6N_4O_2$: C, 47.20; H, 3.39; N, 31.46. Found: C, 47.14; H, 3.55; N, 31.41. The ir showed bands for NH in the region 3340-2650 cm^{-1}, and two C=O's at 1730, 1680 cm^{-1}. The ms showed m/z (rel. int. %): 178 M^+ (100), 150(4), 149(7), 148(53), 147(78), 134(8), 121(35), 120(77), 119(81), 106(11), 105(16), 94(9), 93(40), 92(74), 91(46), 78(55), 77(8), 76(11), 75(17), 70(14), 67(20), 66(39), 65(60), 64(39), 53(22), 52(26), 51(23), 50(15).

Action of Hydroxylamine Hydrochloride on I. Formation of V.

To a solution of N-(phenylsulphonyloxy)quinolinimide (I) (700 mg, 2.3 mmol) in dry pyridine (5 ml), hydroxylamine hydrochloride (640 mg, 9.2 mmol) was added. The reaction mixture was stirred at room temperature for 1 h and the solvent was removed under vacuo. The oily residue formed was washed with water and with ethanol. The solid formed was filtered off, dried and crystallized from acetic acid to give (305 mg, 1.7 mmol , 74%) of 3-hydroxypyrido[3,2-d]pyrimidine-2,4(1H)-dione (V), mp 300-305°C.Anal. Calcd. for $C_7H_5N_3O_3$. N, 23.46. Found:N, 23.06. The ir showed br bands for OH and NH in the region 3140-2720 cm^{-1} and for C=O's at 1740-1670 cm^{-1}. The mass spectrum showed m/z (rel. int. %): 179 M^+ (68), 163 (21), 147 (100), 120 (17), 119 (34), 93(18), 92(12), 91(16), 78(5), 73(7),66(5), 65(8), 64(9).

Action of Primary Aromatic Ammines on I. Formation of VIa-c.

The primary aromatic amines (4.0 mmol) was added with stirring to a suspension of N-(phenylsulphonyloxy)quinolinimide (I) (1.0 mmol) in dry benzene at room temperature. The reaction mixture was stirred for 6 h , then the solvent was removed under vacuo. The solid product was washed with ethanol and purified on a silica gel column using ether as an eluent to give sym-N-2-(arylcarbamoyl)-3-pyridyl-N'-arylureas (VIa-c) as colourless solids (cf. Table 1). The ir spectra showed the presence of NH in the region 3350-3180 cm^{-1}, and C=O in the region 1660-1640 cm^{-1}.

Table 1

Comp. No.	mp °C	Yield %	Mol. Formula	Mol. Wt.	Analysis	Found	Calcd.
VIa	197-98	88	$C_{19}H_{16}N_4O_2$	332.2	C%	68.61	68.67
					H%	4.78	4.82
					N%	16.93	16.86
VIb	201-2	90	$C_{21}H_{20}N_4O_2$	360.4	C%	70.00	69.98
					H%	5.59	5.59
					N%	15.56	15.54
VIc	210-11	95	$C_{21}H_{20}N_4O_4$	392.4	C%	64.12	64.28
					H%	5.18	5.13
					N%	14.23	14.28

Action of Heat on VIa-c. Formation of VIIa-c.

sym-N-2-(Arylcarbamoyl)-3-pyridyl-N'-arylurea (VI) (200 mg) was heated under reduced pressure (1.5 mm) at 200-220°C for 2 h. The solid formed was cooled, washed with ethanol and crystallized from ethanol to give 3-arylpyrido[3,2-d]pyrimidine-2,4-(1H)-diones (VIIa-c) (cf. Table 2). The ir spectra revealed the presence of NH at 3210-3125 cm^{-1} and two C=O's at 1745-1735, 1670 cm^{-1}.

Table 2

Comp. No.	mp °C	Yield %	Mol. Formula	Mol. Wt.		Analysis Found	Calcd.
VIIa	>340	75	$C_{13}H_9N_3O_2$	239.2	C%	64.98	65.27
					H%	3.76	3.79
					N%	17.71	17.55
VIIb	338-42	75	$C_{14}H_{11}N_3O_2$	253.2	C%	66.80	66.38
					H%	4.26	4.37
					N%	16.45	16.59
VIIc	325-30	73	$C_{14}H_{11}N_3O_3$	269.3	C%	62.38	62.44
					H%	4.09	4.11
					N%	15.62	15.60

Action of Alcohols on I. Formation of VIIIa,b.

N-(Phenylsulphonyloxy)quinolinimide (I) (1.3 mmol) was refluxed with ethanol and/or ethanol (100 ml) in presence of few drops of pyridine for 2 h. The solvent was removed under vacuo, and the solid formed was crystallized from petroleum ether to give alkyl -(3-alkoxycarbonylamino)-2-pyridine carboxylate (VIIIa,b) as colourless crystals.

Compound VIIIa, mp 80-81°C, yield 65%. Anal. Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.42; H, 5.92; N, 11.76. Found: C, 55.39; H, 5.77, N, 11.87. The ir spectrum revealed the presence of NH at 3220 cm^{-1}, and of C=O at 1725, 1685 cm^{-1}. Compound VIIIb, mp 134-135°C, yield 88%. Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.42; H, 4.79; N, 13.33. Found: C, 51.41; H, 4.76; N, 13.33. The ir spectrum showed the presence of NH at 3300 and C=O at 1770, 1700 cm^{-1}.

Reaction of Ethyl-(3-ethoxycarbonylamino)-2-pyridine Carboxylate (VIIa) with Aromatic Amines. Formation of 3-Arylpyrido[3,2-d]pyrimidine-2,4(1H)-diones (VIIa-c).

VIIa (1.0 mmol) was heated with the aromatic amines (4 mmol) at 200-220°C for 2 h. The solid formed was cooled, washed with ethanol and recrystallized from ethanol to give VIIIa-c.

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Received, 17th March, 1986