Synthesis of Amino-5-arylsulfonylpyrimidines (1)

Arthur A. Santilli, Murray D. Rosenberg, T. S. Osdene and Scott J. Childress

Research and Development Division, Wyeth Laboratories, Inc.,
Philadelphia, Pennsylvania 19101

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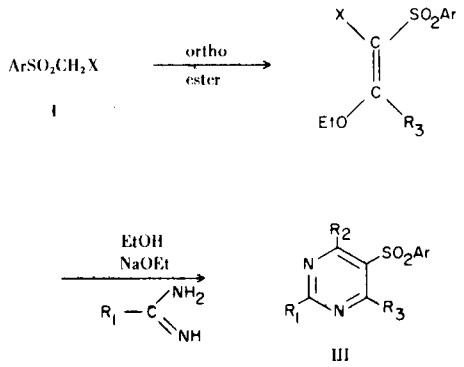
Several new 4-amino-5-arylsulfonylpyrimidines were prepared *via* the reaction of various α-(ethoxymethylene)arylsulfonylacetonitriles with guanidine or variously substituted amidines (Table II). 2,4-Diamino-5-(*p*-chlorophenylsulfonyl)pyrimidine (IIIg), a typical example, was prepared from the reaction of 2-(*p*-chlorophenylsulfonyl)-3-ethoxyacrylonitrile (IId) with guanidine in refluxing ethanol containing sodium ethoxide. With proper substitution of the ethoxymethylene intermediate, the method was found suitable for the preparation of other compounds having either a hydroxy or methyl group at the 4-position of the 5-arylsulfonylpyrimidine. The fluoro group in 2,4-diamino-5-(*p*-fluorophenylsulfonyl)pyrimidine (IIIx) was successfully replaced by nucleophilic reagents such as sodium ethoxide, *N*-methylpiperazine and *N,N*-diethylethylenediamine. Attempts at direct displacement of fluorine by ammonia at 190° were unsuccessful.

Relatively few reports have appeared in the literature on the synthesis of 5-arylsulfonyl or 5-alkylsulfonylpyrimidines which contain amino groups at other positions of the pyrimidine nucleus. The synthetic route to these types of compounds has generally been limited to the oxidation of the corresponding 5-arylthio or 5-alkylthiopyrimidines. Some of the oxidizing agents which have been used for this purpose are chromic acid in glacial acetic acid (2), hydrogen peroxide in acetic acid (3), potassium permanganate (4), and hydrogen peroxide in acetic anhydride (5). It is generally necessary to protect the amino function by acetylation before oxidation is effected. In many instances, "abnormal" products have been reported (2,6,7), and the yields have not always been satisfactory.

The synthesis of pyrimidines by the reaction of amidines or guanidine with various ethxoymethylene compounds such as diethyl ethoxymethylenemalonate (8), ethyl ethoxymethylenecyanoacetate (9), or ethoxymethylenemalononitrile (10) has been known for a number of years. We have extended this type of reaction to the use of α-(ethoxymethylene)arylsulfonylacetonitriles as starting materials for the direct synthesis of 4-amino-5-arylsulfonylpyrimidines (11,12). The products generally are obtained in good yield and are free of the undesirable features associated with the oxidative methods referred to above.

The key α-(ethoxymethylene)arylsulfonylacetonitriles IIa-g (Table I) were prepared by the reaction of the corresponding arylsulfonylacetonitriles with triethyl orthoformate. For example treatment of *p*-chlorophenylsulfonylacetonitrile with triethyl orthoformate afforded 2-(*p*-chlorophenylsulfonyl)-3-ethoxyacrylonitrile (IId). When the ortho ester triethyl orthopropionate was used, 2-(*p*-chlorophenylsulfonyl)-3-ethoxy-2-pentenenitrile (IIh) was obtained. The reaction of *p*-chlorophenylsulfonyl-2-propanone with triethyl orthoformate under the usual conditions gave [1-(*p*-chlorophenylsulfonyl)-2-ethoxy]-vinyl methyl ketone (IIi).

SCHEME I (a)



III

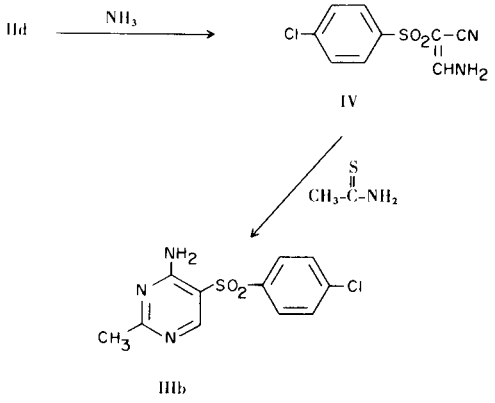
(a) See Tables I and II for definition of Ar, X, R_1, R_2 and R_3.

In a typical example, IId (prepared as described above) was allowed to react with one equivalent of guanidine hydrochloride in refluxing ethanol containing sodium ethoxide. The product, obtained in 94% yield, was 2,4-diamino-5-(*p*-chlorophenylsulfonyl)pyrimidine (IIIg). Other examples of amino-5-arylsulfonylpyrimidines prepared generally by this method are outlined in Scheme I

and are specifically designated in Table II. Treatment of IIIg with boiling acetic anhydride resulted in acetylation of both amino groups, giving 2,4-diacetamido-5-(*p*-chlorophenylsulfonyl)pyrimidine (IIIj).

In one example, a departure from the general synthesis was used for preparing 4-amino-5-(*p*-chlorophenylsulfonyl)-2-methylpyrimidine (IIIb). The process is shown in Scheme II. Treatment of IId with ammoniacal ethanol afforded 3-amino-2-(*p*-chlorophenylsulfonyl)acrylonitrile (IV). The reaction of the latter product with thioacetamide afforded IIIb.

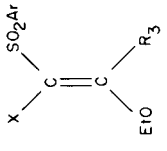
SCHEME II



An attempt to prepare 4-amino-5-(*p*-chlorophenylsulfonyl)-2-hydroxypyrimidine (IIIk) directly by the reaction of IId with urea failed (Scheme III). It was found however, that IIIk could be successfully prepared in two steps. The reaction of IId with *S*-methylisothiourea under the conditions used to prepare IIIg afforded 4-amino-5-(*p*-chlorophenylsulfonyl)-2-methylthiopyrimidine (IIIe). Treatment of IIIe in hydrochloric acid with chlorine gave the desired IIIk in moderate yield. The presence of an intense carbonyl band at 5.94 μ in the infrared spectrum of this compound indicates it must exist to a high degree in the tautomeric lactam form (13).

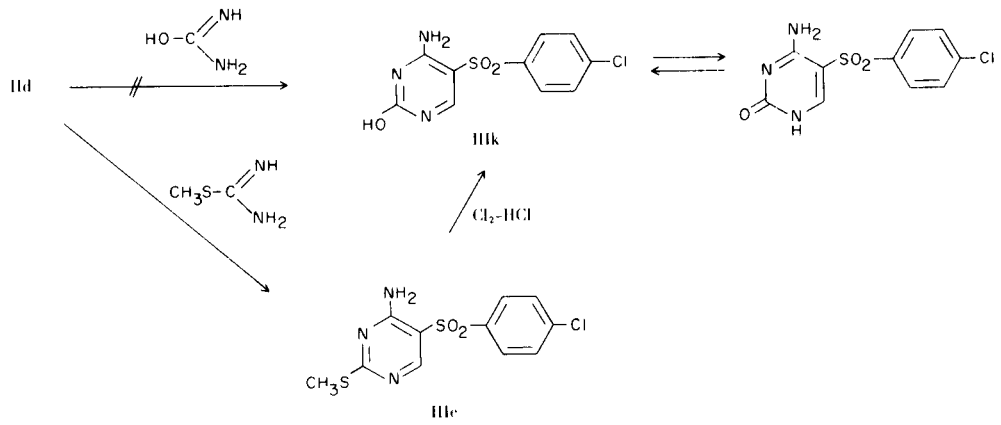
An isomeric pyrimidine, IIIh, in which the hydroxy group is in the 4-position of the pyrimidine nucleus, was prepared (Scheme IV), starting with ethyl *p*-chlorophenylthioacetate (V). Oxidation of this ester with hydrogen peroxide in glacial acetic acid gave mainly ethyl *p*-chlorophenylsulfonylacetate (VI). Treatment of the latter product with triethyl orthoformate under the usual conditions afforded ethyl 2-(*p*-chlorophenylsulfonyl)-3-ethoxyacrylate (VII), which upon reaction with guanidine gave 2-amino-5-(*p*-chlorophenylsulfonyl)-4-hydroxypyrimidine (IIIh). Again, the presence of an intense carbonyl band at 5.99 μ in the infrared spectrum of this compound indicates that the tautomeric lactam form must offer a

TABLE I



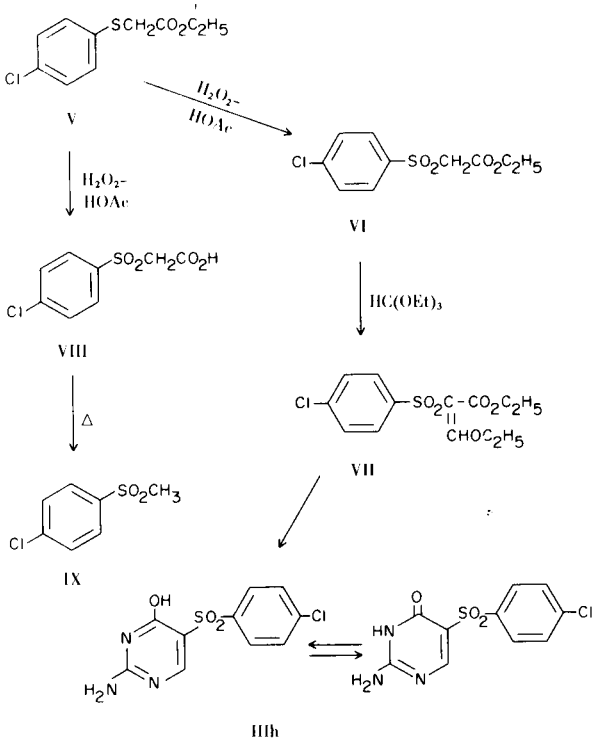
Compound	R_3	Ar	X	M.p., °C	Yield %	Recryst. Solvent	Empirical Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
IIa	H	C_6H_5	CN	73 - 74	96	ether	$C_{11}H_{11}NO_3S$	55.68	4.67	5.90	55.74	4.68	6.11
b	H	*m*-$CH_3C_6H_4$	CN	74 - 75	50	ethanol-water	$C_{12}H_{13}NO_3S$	57.37	5.22	5.58	57.37	5.19	5.54
c	H	*p*-$CH_3C_6H_4$	CN	109 -112	97	methanol	$C_{12}H_{13}NO_3S$	57.37	5.22	5.58	57.19	4.92	5.65
d	H	*p*-ClC_6H_4	CN	121.5-122	98	ethanol	$C_{11}H_{10}ClNO_3S$	48.62	3.71	5.16	48.91	3.63	5.04
e	H	*p*-FC_6H_4	CN	105 -106	97	ethanol	$C_{11}H_{10}FNO_3S$	51.76	3.95	5.49	52.02	4.04	5.51
f	H	β-naphthyl	CN	132 -133	73	ethanol	$C_{15}H_{13}NO_3S$	62.71	4.56	4.88	62.67	4.77	4.83
g	H	*p*-$AcNHC_6H_4$	CN	197.5-199	63	ethanol	$C_{13}H_{14}N_2O_4S$	53.06	4.80	9.52	53.12	4.88	9.64
h	C_2H_5	*p*-ClC_6H_4	CN	106.5-108	95	methanol	$C_{13}H_{14}ClNO_3S$	52.08	4.71	4.67	51.87	4.54	4.79
i	H	*p*-ClC_6H_4	$COCH_3$	112 -113	100	ethanol	$C_{12}H_{13}ClO_4S$	49.91	4.54		50.00	4.62	

SCHEME III



significant contribution to the ground state of the molecule (13). In addition to the main product, VI, in the oxidation reaction of V, two other products were also isolated, 2-(*p*-chlorophenylsulfonyl)acetic acid (VIII) and *p*-chlorophenyl methyl sulfone (IX). Apparently a partial hydrolysis of V occurred, followed by some decarboxylation, possibly during distillation.

SCHEME IV

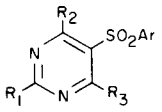


The reaction of 2,4-diamino-5-(*p*-fluorophenylsulfonyl)-pyrimidine (IIIx) with various nucleophilic reagents was studied (Scheme V). In these reactions the fluoro group was displaced by the nucleophile. For example, treatment of IIIx with sodium ethoxide in refluxing ethanol afforded 2,4-diamino-5-(*p*-ethoxyphenylsulfonyl)pyrimidine (IIIa′). In similar fashion, the reaction of IIIx with *N*-methylpiperazine and *N,N*-diethylethylenediamine afforded IIIb′ and IIIc′, respectively. These displacement reactions must be greatly facilitated by the strong electron-withdrawing power of the sulfone group located *para* to the carbon bearing the fluorine atom. The electron deficiency thus created at this center makes it susceptible to attack by various nucleophilic reagents. Efforts to use this type of reaction for the preparation of 2,4-diamino-5-(*p*-sulfanilyl)-pyrimidine (IIId′) by heating IIIx with ammonia in an autoclave at 190° for several hours were unsuccessful. The original pyrimidine was recovered unchanged.

A successful synthesis of IIId′ was realized, starting from the reaction of 2-(*p*-acetamidophenylsulfonyl)-3-ethoxyacrylonitrile (IIg) with guanidine. The product thus formed, 5-(*p*-acetamidophenylsulfonyl)-2,4-diamino-pyrimidine (IIIy), was subjected to acid hydrolysis to afford the desired pyrimidine (IIId′). 4-Amino-2-phenyl-5-(*p*-sulfanilyl)pyrimidine (IIIe′) was prepared in similar fashion *via* the reaction of IIg with benzamidine, followed by hydrolysis of the product.

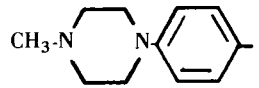
Work in this report has centered mainly on the syntheses of 5-arylsulfonylpyrimidines having an amino group at the 4-position of the pyrimidine ring. With proper substitution of the ethoxymethylene intermediate, a 5-arylsulfonyl-4-hydroxypyrimidine (IIIh) was prepared. Finally, one example of a 4-alkyl-5-arylsulfonylpyrimidine was provided by the reaction of [1-(*p*-chlorophenylsulfonyl)-2-ethoxy]vinyl methyl ketone (IIi) with guanidine under the usual conditions. The product thus afforded was 2-amino-5-(*p*-chlorophenylsulfonyl)-4-methylpyrimidine (IIIc).

TABLE II



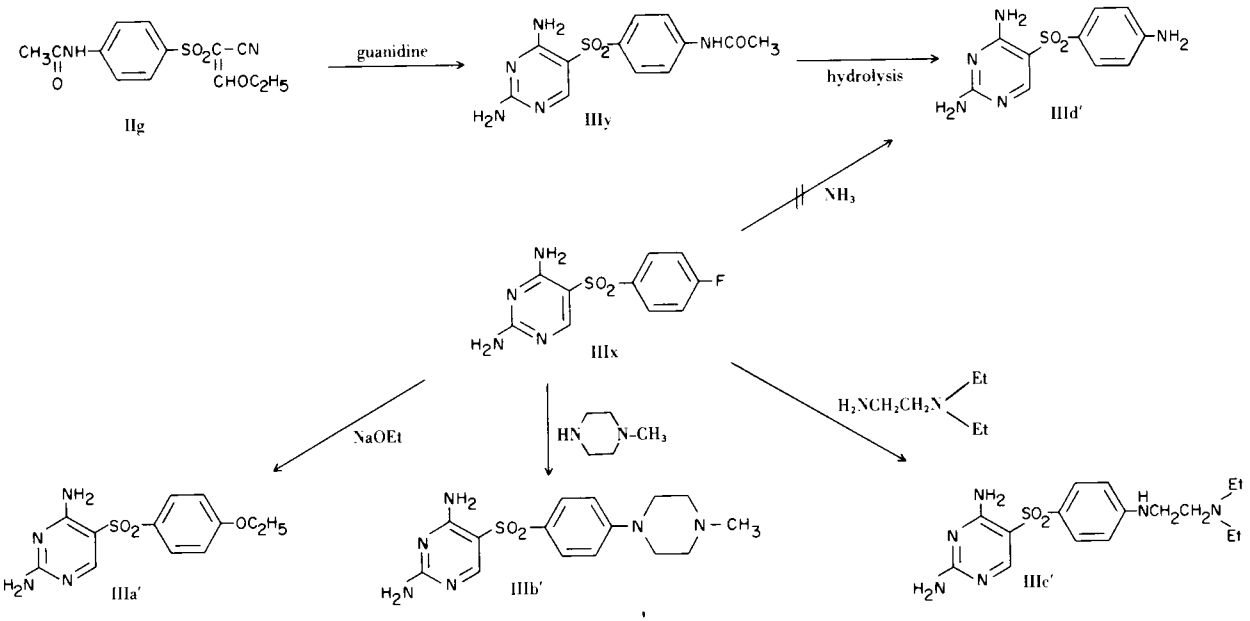
Compound	R_1	R_2	Ar	R_3	M.p., °C	Yield %	Recryst. Solvent	Empirical Formula	Calcd., % C	H	N	Found, % C	H	N
IIIa	H	NH_2	*p*-ClC_6H_4	H	178 -179	76	ethanol	$C_{10}H_8ClN_3O_2S$	44.53	2.99	15.58	44.64	2.93	15.29
b	CH_3	NH_2	*p*-ClC_6H_4	H	191 -192	33	ethanol	$C_{11}H_{10}ClN_3O_2S$	46.56	3.55	14.81	46.20	3.40	14.84
c	NH_2	CH_3	*p*-ClC_6H_4	H	250 -251	71	ethanol	$C_{11}H_{10}ClN_3O_2S$	46.56	3.55	14.81	46.52	3.25	14.55
d	C_3H_7	NH_2	*p*-ClC_6H_4	H	157 -158	87	methanol	$C_{13}H_{14}ClN_3O_2S$	50.08	4.53	13.48	50.01	4.42	13.21
e	CH_3S	NH_2	*p*-ClC_6H_4	H	182 -183	63	benzene	$C_{11}H_{10}ClN_3O_2S_2$	41.84	3.19	13.31	42.21	3.08	13.28
f	C_6H_5	NH_2	*p*-ClC_6H_4	H	220 -222	100	ethanol	$C_{16}H_{12}ClN_3O_2S$	55.57	3.50	12.15	55.33	3.20	12.49
g (a)	NH_2	NH_2	*p*-ClC_6H_4	H	262 -263	94	DMF-water	$C_{10}H_9ClN_4O_2S$	42.18	3.19	19.68	42.25	3.16	19.88
h (b)	NH_2	OH	*p*-ClC_6H_4	H	347 -348 d	77		$C_{10}H_8ClN_3O_3S$	42.04	2.82	14.71	42.02	2.67	14.74
i	NH_2	NH_2	*p*-ClC_6H_4	C_2H_5	174.5-176	18	benzene	$C_{12}H_{13}ClN_4O_2S$	46.08	4.19	17.91	45.97	4.16	18.21
j	CH_3CONH	CH_3CONH	*p*-ClC_6H_4	H	219 -220	80	2-ethoxyethanol-water	$C_{14}H_{13}ClN_4O_4S$	45.59	3.55	15.19	45.57	3.76	15.38
k	OH	NH_2	*p*-ClC_6H_4	H	335 -337 d	35	DMF	$C_{10}H_8ClN_3O_3S$	42.04	2.82	14.71	42.26	2.71	14.61
l	NH_2	NH_2	C_6H_5	H	304 -306	78	DMF-water	$C_{10}H_{10}N_4O_2S$	47.99	4.03	22.39	48.10	4.19	22.21
m	H	NH_2	*p*-$CH_3C_6H_4$	H	169 -170	60	ethanol	$C_{11}H_{11}N_3O_2S$	53.00	4.46	16.86	53.02	4.39	16.87
n	C_6H_5	NH_2	*p*-$CH_3C_6H_4$	H	180 -181	93	ethanol	$C_{17}H_{15}N_3O_2S$	62.75	4.65	12.92	62.45	4.37	12.96
o	CH_3S	NH_2	*p*-$CH_3C_6H_4$	H	178 -179	40	benzene	$C_{12}H_{13}N_3O_2S_2$	48.80	4.40	14.22	48.74	4.38	13.96
p (c)	NH_2	NH_2	*p*-$CH_3C_6H_4$	H	285 -287	98	DMSO-water	$C_{11}H_{12}N_4O_2S$	49.99	4.58	21.19	50.07	4.54	20.96
q	H	NH_2	*m*-$CH_3C_6H_4$	H	168 -170	97	EtOAc-petroleum ether	$C_{11}H_{11}N_3O_2S$	53.00	4.46	16.86	53.24	4.58	16.96
r	C_6H_5	NH_2	*m*-$CH_3C_6H_4$	H	167 -168	70	ethanol	$C_{17}H_{15}N_3O_2S$	62.75	4.65	12.92	62.87	4.46	13.19
s	NH_2	NH_2	*m*-$CH_3C_6H_4$	H	254 -255	49	DMF-water	$C_{11}H_{12}N_4O_2S$	49.99	4.58	21.19	49.83	4.53	21.32
t	*m*-ClC_6H_4	NH_2	*m*-$CH_3C_6H_4$	H	171 -172	81	ethanol-water	$C_{17}H_{14}ClN_3O_2S$	56.74	3.92	11.68	56.52	3.73	11.42
u	H	NH_2	β-naphthyl	H	206 -208	70	ethanol	$C_{14}H_{11}N_3O_2S$	58.93	3.89	14.73	58.66	3.92	15.04
v	C_6H_5	NH_2	β-naphthyl	H	193 -194	61	ethanol	$C_{20}H_{15}N_3O_2S$	66.46	4.18	11.63	66.39	4.10	11.72
w	NH_2	NH_2	β-naphthyl	H	306 -307	50	2-ethoxyethanol-water	$C_{14}H_{12}N_4O_2S$	55.99	4.03	18.66	56.25	4.31	18.82
x	NH_2	NH_2	*p*-FC_6H_4	H	233 -235	50	ethanol	$C_{10}H_9FN_4O_2S$	44.77	3.38	20.89	44.76	3.11	20.63
y	NH_2	NH_2	*p*-$AcNHC_6H_4$	H	283 -284	52	DMF-water	$C_{12}H_{13}N_5O_3S$	46.90	4.26	22.79	47.01	4.54	22.77

TABLE II (continued)

Compound	R_1	R_2	Ar	R_3	M.p., °C	Yield %	Recryst. Solvent	Empirical Formula	Calcd., % C	H	N	Found, % C	H	N
z	C_6H_5	NH_2	*p*-$AcNHC_6H_4$	H	251 -252	41	ethanol-water	$C_{18}H_{16}N_4O_3S$	58.68	4.38	15.21	58.43	4.18	15.4
a′	NH_2	NH_2	*p*-$EtOC_6H_4$	H	261 -262	96	ethanol	$C_{12}H_{14}N_4O_3S$	48.97	4.79	19.04	48.74	4.50	18.77
b′	NH_2	NH_2		H	245 -247	99	ethanol	$C_{15}H_{20}N_6O_2S$	51.71	5.79	24.12	51.65	5.71	23.90
c′	NH_2	NH_2	*p*-$(Et_2NCH_2CH_2NH)C_6H_4$	H	173 -174	67	ethanol	$C_{16}H_{24}N_6O_2S$	52.72	6.64	23.06	52.46	6.42	22.82
d′	NH_2	NH_2	*p*-$H_2NC_6H_4$	H	260 -261	67	DMF-water	$C_{10}H_{11}N_5O_2S$	45.27	4.18	26.40	45.31	4.03	26.32
e′	C_6H_5	NH_2	*p*-$H_2NC_6H_4$	H	208 -210	63	acetone	$C_{16}H_{14}N_4O_2S$	58.88	4.32	17.17	59.19	4.32	17.14

(a) DMF = *N,N*-dimethylformamide. (b) Purified by dissolving in 10% sodium hydroxide and reprecipitating by acidification with glacial acetic acid. (c) DMSO = dimethylsulfoxide.

SCHEME V



Several of the pyrimidines described in this report were screened for antibacterial activity, since they resemble structurally related, clinically useful agents, *e.g.* sulfamethazine or sulfadimethoxine. Although a number of the compounds were active, none was sufficiently interesting to merit further clinical evaluation. Several exhibited a mild analgetic and hypotensive action in rats.

EXPERIMENTAL

Melting points were taken using a Thomas-Hoover capillary melting point apparatus and are uncorrected. The infrared spectra were determined in potassium bromide discs using a Perkin-Elmer spectrophotometer (Model 21). The observed spectra are in accord with the assigned structures, and for brevity only essential spectral features are given for key compounds.

Several of the arylsulfonylacetonitriles used for the preparation of the ethoxymethylene intermediates (Table I) have been previously described. These are: phenylsulfonylacetonitrile (14), *m* and *p*-tolylsulfonylacetonitrile (14), *p*-chlorophenylsulfonylacetonitrile (14), β-naphthylsulfonylacetonitrile (14), and *p*-acetamidophenylsulfonylacetonitrile (15). (*p*-Chlorophenylsulfonyl)-2-propanone has also been reported (16).

With the exception of *m*-chlorobenzamidine hydrochloride (17), all amidines were commercially available.

2-(*p*-Chlorophenylsulfonyl)-3-ethoxyacrylonitrile (IId).

A mixture of 32.8 g. of *p*-chlorophenylsulfonylacetonitrile, 71.6 g. of triethyl orthoformate and 1 ml. of glacial acetic acid was stirred in a flask equipped with a distillation assembly and heated in an oil bath to 140°. This temperature was maintained for 3.5 hours, during which time 27 ml. of alcohol was collected. The excess triethyl orthoformate was then removed on a rotary evaporator *in vacuo*. The residual oil crystallized on cooling, affording 40 g. of product, m.p. 108-111°. The analytical sample, m.p. 121.5-122°, was obtained by recrystallization from ethanol; ir 4.54 (CN), 6.18 (C=C), 7.51, 8.60 μ (SO_2).

2,4-Diamino-5-(*p*-chlorophenylsulfonyl)pyrimidine (IIIg).

To a stirred solution of 0.3 g. of sodium in 30 ml. of absolute ethanol was added 1.43 g. of guanidine hydrochloride, followed by 4.07 g. of IId. The reaction mixture was heated under reflux for 4 hours and then filtered under suction. The 4.2 g. of solid which was collected on the filter was put into 50 ml. of warm water to dissolve the sodium chloride present. The residual solid which was collected on refiltering the mixture amounted to 4.0 g., m.p. 259-262°. Recrystallization from aqueous *N,N*-dimethylformamide afforded 3.6 g. of product, m.p. 262-263°; ir 2.95, 3.06, 3.22 (NH), 7.77, 8.73 μ (SO_2).

2,4-Diacetamido-5-(*p*-chlorophenylsulfonyl)pyrimidine (IIIj).

A mixture of 2.84 g. of IIIi and 19 ml. of acetic anhydride was heated under reflux for 2 hours. The reaction was cooled in ice, whereupon a crystalline product separated. This was collected on a filter and weighed 2.95 g. Recrystallization from aqueous 2-ethoxyethanol afforded the product, m.p. 219-220°; ir 3.14 (NH), 5.85 (C=O), 7.64, 8.70 μ (SO_2).

3-Amino-2-(*p*-chlorophenylsulfonyl)acrylonitrile (IV).

A mixture of 5.4 g. of IId in 25 ml. of a 30% ethanolic ammonia solution was heated for 5 minutes on a steam bath. A solid formed which amounted to 4.1 g., m.p. 208-210.5°. Recrystallization from aqueous ethanol afforded the analytical sample, m.p. 215-216°; ir 3.00, 3.14 (NH_2), 4.56 (CN), 6.03 (C=C), 7.62, 8.63 μ (SO_2).

Anal. Calcd. for $C_9H_7N_2ClO_2S$: C, 44.54; H, 2.91; N, 11.54. Found: C, 44.68; H, 2.89; N, 11.78.

4-Amino-5-(*p*-chlorophenylsulfonyl)-2-methylpyrimidine (IIIb).

To a solution of 0.23 g. of sodium dissolved in 30 ml. of absolute ethanol was added 0.78 g. of thioacetamide, followed by 2.4 g. of IV. The mixture was stirred and heated under reflux for 1 hour. The hot solution was filtered and the filtrate was cooled in ice, giving 0.8 g. of product, m.p. 187-189°. Recrystallization from ethanol afforded the analytical sample, m.p. 191-192°; ir 2.96, 3.10 (weak) (NH), 7.59, 8.75 μ (SO_2).

4-Amino-5-(*p*-chlorophenylsulfonyl)-2-hydroxypyrimidine (IIIk).

To a solution of 40 ml. of concentrated hydrochloric acid and 600 ml. of water was added 3.16 g. of 4-amino-5-(*p*-chlorophenylsulfonyl)-2-methylthiopyrimidine (IIIe). A slow stream of chlorine gas was led into the solution for a period of 1.5 hours. The reaction mixture was kept overnight at room temperature and then filtered under suction, affording 3.5 g. of solid. This material was dissolved in 20 ml. of 10% sodium hydroxide solution. The solution was filtered and the filtrate was neutralized with concentrated hydrochloric acid. The solid which precipitated out of solution amounted to 1.0 g. Recrystallization of this product from aqueous *N,N*-dimethylformamide gave 0.7 g. of IIIk, m.p. 335-337°; ir 3.81 (NH or OH), 5.94 (lactam C=O), 7.80, 8.42 μ (SO_2).

Ethyl *p*-Chlorophenylsulfonylacetate (VI).

To a solution of 173 g. of ethyl *p*-chlorophenylthioacetate (18) in 224 ml. of glacial acetic acid was added 224 ml. of 30% hydrogen peroxide solution. The reaction mixture was heated on a steam bath for 4 hours and allowed to stand overnight at room temperature. On being cooled in ice, the mixture separated into an aqueous phase and an oil phase (92.2 g.). The aqueous portion was poured onto 100 g. of ice and allowed to stand for 0.5 hour, during which time a second phase separation occurred. The aqueous phase from this latter separation was washed twice with 50 ml. of benzene and the benzene solution was added to the 92.2 g. of oil which had previously separated.

The oily residue from the second separation crystallized, giving 48.8 g. of a solid, m.p. 113-116°. Recrystallization from benzene raised the melting point to 120-122°. The product was found to be soluble in dilute sodium bicarbonate solution and was identified as *p*-chlorophenylsulfonylacetic acid (VIII), lit. (19) m.p. 122°; ir 3.40-4.10 broad (acid OH), 5.84 (C=O), 7.55, 8.77 μ (SO_2).

Anal. Calcd. for $C_8H_7ClO_4S$: C, 40.95; H, 3.01; Cl, 15.11; S, 13.66. Found: C, 41.02; H, 2.96; Cl, 15.00; S, 13.4.

The 92.2 g. of oil and the benzene extracts were washed twice with 50 ml. portions of water and the organic phase was dissolved in 300 ml. of ether. The ether solution was dried over magnesium sulfate and filtered and the filtrate was evaporated to dryness. The oily residue was distilled through a Claisen head *in vacuo*.

The first fraction that was collected distilled at 153-166° (1.8 mm). On standing, this material crystallized, affording 3.5 g. of a solid, m.p. 93-95°, identified as *p*-chlorophenyl methyl sulfone (IX), lit. (20) m.p. 96°; ir 7.60-8.75 μ (SO_2).

The second fraction (64.8 g.), which distilled at 179-180° (2.0 mm), was identified as VI (18); ir 5.75 (C=O), 7.54, 8.67 μ (SO_2).

Anal. Calcd. for $C_{10}H_{11}ClO_4S$: C, 45.72; H, 4.22; S, 12.2. Found: C, 45.57; H, 4.12; S, 11.9.

Ethyl 2-(*p*-Chlorophenylsulfonyl)-3-ethoxyacrylate (VII).

A stirred solution of 39.4 g. of VI, 72 g. (0.485 mole) of triethyl orthoformate and 1 ml. of glacial acetic acid was heated to 170° for 5 hours in a flask equipped with a distillation assembly. During this time 24 ml. of distillate was collected. The excess triethyl orthoformate was removed *in vacuo* on a rotary evaporator, giving 47 g. of an oil identified as VII. Difficulty was experienced in purifying VII by distillation. It was used satisfactorily without purification for the preparation of IIIh.

2-Amino-5-(*p*-chlorophenylsulfonyl)-4-hydroxypyrimidine (IIIh).

To a stirred solution of 0.97 g. of sodium metal in 40 ml. of absolute ethanol was added 1.91 g. of guanidine hydrochloride. After 25 minutes, 6.35 g. of VII was added to the reaction mixture, which was then heated under reflux for 3 hours. The excess ethanol was removed on a rotary evaporator *in vacuo*. The residual solid was dissolved in 50 ml. of water and the solution was filtered. Acidification of the filtrate to a *p*H of 4 with concentrated hydrochloric acid resulted in the deposition of 4.4 g. of solid, m.p. 331-333° dec. This material was dissolved in 10% sodium hydroxide solution and the solution was treated with charcoal and filtered. Acidification of the filtrate with glacial acetic acid resulted in the deposition of 2.3 g. of IIIh, m.p. 347-348° dec.; ir 3.09, 3.34 (NH or OH), 5.99 (lactam C=O), 7.80, 8.76 μ (SO_2).

2-(*p*-Acetamidophenylsulfonyl)-3-ethoxyacrylonitrile (IIg).

A mixture of 9.55 g. of (*p*-acetamidophenylsulfonyl)acetonitrile, 38 g. of triethyl orthoformate and 4.2 g. of acetic anhydride was heated for 3 hours at 150-160° in a flask equipped with a distilling head. A total of 19 ml. of distillate was collected. The reaction mixture was cooled and filtered under suction, affording 7.4 g. of solid, m.p. 191-193°. Recrystallization from ethanol raised the m.p. to 197.5-199°; ir 3.05 (NH), 4.53 (CN), 5.90 (C=O), 6.55 (amide II), 7.55, 8.61 μ (SO_2).

5-(*p*-Acetamidophenylsulfonyl)-2,4-diaminopyrimidine (IIIy).

To a stirred solution of 0.97 g. of sodium in 30 ml. of absolute ethanol was added 2.18 g. of guanidine hydrochloride and (after 5 minutes of stirring) 5.9 g. of IIg. The reaction mixture was heated under reflux for 2 hours, cooled and filtered. A brown solid was collected which amounted to 32 g., m.p. 264-268°. This material was washed with water and recrystallized twice from aqueous *N,N*-dimethylformamide, giving 1.1 g. of IIIy, m.p. 283-284°; ir 2.95, 3.05, 3.22 (NH), 5.95 (C=O), 7.82, 8.80 μ (SO_2).

5-(*p*-Acetamidophenylsulfonyl)-4-amino-2-phenylpyrimidine (IIIz).

This compound was prepared in identical fashion, using 0.99 g. of sodium in 80 ml. of absolute ethanol and 5.95 g. of benzamidine hydrochloride, followed by 11.2 g. of IId. There was obtained 5.7 g. IIIz, m.p. 239-241°. The analytical sample, m.p. 251-252°, was obtained by recrystallization from aqueous ethanol; ir 2.93, 3.02 (NH), 5.92 (C=O), 7.56, 8.72 μ (SO_2).

2,4-Diamino-5-sulfanilylpyrimidine (IIId').

A mixture of 0.35 g. of IIIy, 50 ml. of absolute ethanol and 37.5 ml. of concentrated hydrochloric acid was heated under reflux for 4 hours and then cooled in ice. Filtration of the mixture afforded 0.4 g. of solid, m.p. 283-285° dec. This material was triturated with 20 ml. of concentrated ammonium hydroxide and the mixture was filtered. The white powder thus obtained amounted to 0.3 g., m.p. 259-263°. Recrystallization from aqueous *N,N*-dimethylformamide afforded 0.2 g. of IIId', m.p. 260-261°; ir 2.98, 3.21 (NH), 7.88, 8.79 μ (SO_2).

4-Amino-2-phenyl-5-sulfanilylpyrimidine (IIIe').

This compound was obtained in identical fashion, starting with a mixture of 5.2 g. of IIIz and 23 ml. of concentrated hydrochloric acid solution. There was obtained 2.9 g. of IIIe' m.p. 208-210°; ir 2.95, 3.02, 3.20 (NH), 7.72, 8.75 μ (SO_2).

p-Fluorophenylthioacetonitrile.

To a stirred solution of sodium ethoxide, prepared by reacting 4.6 g. of sodium metal in 200 ml. of ethanol, was added 25.6 g. of *p*-fluorobenzenethiol. The reaction mixture was cooled to 0-10° in ice and 15.1 g. of chloroacetonitrile was added dropwise. The temperature of reaction was allowed to rise to room temperature. Stirring was continued for an hour and the mixture was filtered under suction. The ethanol was removed from the filtrate in a rotary evaporator under suction. The residual oil crystallized, giving 33.4 g. of product, m.p. 34-38°. The analytical sample, m.p. 34-35°, was obtained by recrystallization from petroleum ether; ir 4.49 μ (CN).

Anal. Calcd. for C_8H_6FNS: C, 57.46; H, 3.62; N, 8.38; S, 19.18. Found: C, 57.76; H, 3.57; N, 8.59; S, 19.2.

p-Fluorophenylsulfonylacetonitrile.

To a solution of 32 g. of *p*-fluorophenylthioacetonitrile in 57.5 g. of glacial acetic acid was added 55 ml. of 30% hydrogen peroxide solution. The reaction mixture was heated on a steam bath for 1 hour and then cooled in ice. Cold water was added until precipitation was complete. The precipitate was collected under suction and amounted to 40 g., m.p. 88.5-89.5°. The analytical sample, m.p. 90-91°, was obtained by recrystallization from ether-petroleum ether; ir 4.46 (CN), 7.60, 8.75 μ (SO_2).

Anal. Calcd. for $C_8H_6FNO_2S$: C, 48.23; H, 3.04; N, 7.03; S, 16.10. Found: C, 48.31; H, 2.95; N, 7.04; S, 16.0.

3-Ethoxy-2-(*p*-fluorophenylsulfonyl)acrylonitrile (IIe).

This compound was prepared from 25.8 g. of *p*-fluorophenylsulfonylacetonitrile, 60 g. of triethyl orthoformate and 3 ml. of glacial acetic acid in the manner described for the preparation of IId. There was obtained 27.1 g. of product; ir 4.53 (CN), 6.14 (sh), 6.21, 6.30, 6.95 (C=C and aromatic C=C), 7.50, 8.60 μ (SO_2).

2,4-Diamino-5-(*p*-fluorophenylsulfonyl)pyrimidine (IIIx).

A mixture of 7.65 g. of IIe, 2.7 g. of guanidine carbonate and 50 ml. of absolute ethanol was stirred and heated under reflux for 5 hours. The reaction mixture was cooled and filtered under suction, affording 4 g. of IIIx, m.p. 232-234°. Recrystallization from ethanol gave 3.2 g. of pure product, m.p. 233-235°; ir 2.92, 3.06, 3.22 (NH), 7.79, 8.75 μ (SO_2).

2,4-Diamino-5-(*p*-ethoxyphenylsulfonyl)pyrimidine (IIIa').

To a solution of 0.46 g. of sodium metal in 50 ml. of absolute ethanol was added 1.8 g. of IIIx. The reaction mixture was heated under reflux for 1 hour, allowed to stand at ambient temperature for 12 hours, and then cooled in ice. The crystalline product which was deposited amounted to 1.9 g., m.p. 258-259°. The analytical sample, m.p. 261-262°, was obtained by recrystallization in ethanol; ir 2.97, 3.09, 3.22 (NH), 7.85, 8.76 μ (SO_2).

2,4-Diamino-5-[*p*-(4-methyl-1-piperazinyl)phenylsulfonyl]pyrimidine (IIIb').

A solution of 3.0 g. of IIIx in 22.0 g. of *N*-methylpiperazine was heated under reflux for 6.5 hours. The excess *N*-methylpiperazine was removed *in vacuo* on a rotary evaporator. To the partially solid residue was added 50 ml. of water. The mixture was then filtered, giving 3.8 g. of product, m.p. 235-249°. Re-

crystallization from ethanol afforded 1.65 g. of IIIb′, m.p. 245-247°; ir 2.97, 3.03 (NH_2), 3.46 (aliphatic CH), 3.64 (N-CH_3), 7.74, 8.75 μ (SO_2).

2,4-Diamino-5-(*N*-[2-(diethylamino)ethyl]sulfanilyl)pyrimidine (IIIc′).

In similar fashion, IIIc′ was prepared from 3.0 g. of IIIx and 11.6 g. of *N,N*-diethylethylenediamine by boiling under reflux for 3 hours. The analytical sample, obtained by recrystallization from ethanol, amounted to 2.7 g., m.p. 173-174°; ir 2.95, 3.05, 3.21 (NH), 3.44 (aliphatic CH), 7.85, 8.72 μ (SO_2).

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REFERENCES

(1) Presented before the Division of Medicinal Chemistry of the 153rd American Chemical Society Meeting, Miami Beach, Fla., April 1967.

(2) W. T. Caldwell and A. N. Sayin, *J. Am. Chem. Soc.*, **74**, 4314 (1952).

(3) I. Kh. Fel'dman, V. M. Merlis and Y. M. Rozanova, *Zh. Obshch. Khim.*, **19**, 1683 (1949); *Chem. Abstr.*, **44**, 1051f (1950).

(4) M. Ohta and R. Sudo, *J. Pharm. Soc. Japan*, **71**, 514 *Chem. Abstr.*, **46**, 4549i (1952).

(5) M. Yanagita and R. Futaki, *J. Pharm. Soc. Japan*, **72**, 236 (1952); *Chem. Abstr.*, **47**, 6424i (1953).

(6) T. B. Johnson and J. M. Sprague, *J. Am. Chem. Soc.*, **60**, 1622 (1938).

(7) K. J. M. Andrews, N. Anand, A. R. Todd and A. Topham, *J. Chem. Soc.*, 2490 (1949).

(8) T. A. Geissman, M. J. Schlatter, I. D. Webb and J. D. Roberts, *J. Org. Chem.*, **11**, 741 (1946).

(9) A. R. Todd and F. Bergel, *J. Chem. Soc.*, 364 (1937).

(10) W. Huber and H. A. Hölscher, *Chem. Ber.*, B **71**, 87 (1938).

(11) A. A. Santilli, T. S. Osdene and S. J. Childress, U. S. Patent 3,553,198 (1971).

(12) E. Habicht and R. Zubiani, U. S. Patent 3,435,035 (1969), have also recently described the preparation of similar pyrimidine sulfones *via* the reaction of ethoxymethylene intermediates with amidines and guanidines.

(13) Although the lactam nature of hydroxy pyrimidines, in general, is well recognized, for simplicity we have retained the system of nomenclature used in D. J. Brown's "The Pyrimidines" (Interscience, New York, N. Y., 1962).

(14) J. Troeger and W. Helle, *J. Prakt. Chem.*, **71**, 225 (1905).

(15) B. R. Baker and M. V. Querry, *J. Org. Chem.*, **15**, 417 (1950).

(16) M. Ohta and R. Sudo, *J. Pharm. Soc. Japan*, **69**, 43 (1949); *Chem. Abstr.*, **44**, 1485 (1950).

(17) T. S. Osdene, A. A. Santilli, L. E. McCardle and M. E. Rosenthale, *J. Med. Chem.*, **9**, 697 (1966).

(18) S. L. Shapiro, I. M. Rose, F. C. Testa and L. Freedman, *J. Am. Chem. Soc.*, **81**, 5646 (1959).

(19) J. Troeger and C. Budde, *J. Prakt. Chem.*, **66**, 146 (1902).

(20) C. J. Miller and S. Smiles, *J. Chem. Soc.*, **127**, 224 (1925); *Chem. Abstr.*, **19**, 1133 (1925).