

## **s-Triazines. Part I. Synthesis and Reactions of Dihalogeno-heteroaryl-s-triazines**

By Jiban K. Chakrabarti,\* Ronald W. Goulding, and Alec Todd, Lilly Research Centre, Ltd., Erl Wood Manor, Windlesham, Surrey

Metallated derivatives of substituted or unsubstituted furans, thiophenes, and pyrroles react with 2,4,6-trichloro-s-triazine (cyanuric chloride) to produce the corresponding 2,4-dichloro-6-(heteroaryl)-s-triazines. The effect of electrophilic substitution (nitration and bromination) on such ring systems is described.

THE preparation of s-triazines carrying C-C linked heteroaryl substituents by methods which involve synthesis of the triazine ring has been described.<sup>1</sup> These syntheses usually lead to triazines having functional groups incorporating O, S, or N on the other carbon atoms. Except in the last case, where a prior hydrolysis to the dioxo-analogue is required, these groups can be halogenated<sup>1a,b,2</sup> to give dihalogeno-heteroaryl-s-triazines. 2,4,6-Trichloro-s-triazine (cyan-

uric chloride) reacts with a phenyl Grignard reagent to give the corresponding dichlorophenyl-s-triazine,<sup>3</sup> but there appears to be no report of the use of a suitable lithiated aromatic species to effect such substitution. We have examined such reactions in the hope that certain 2,4-dihalogeno-heteroaryl-s-triazines, otherwise only obtainable *via* a multi-step procedure, could be made by a one-step synthesis.

We have found that a metallated derivative of a suitably substituted or an unsubstituted furan, thiophen,

<sup>1</sup> (a) Fr.P. 1,387,435/1965 (*Chem. Abs.*, 1965, **62**, 16,276); (b) H. Eilingsfeld and H. Scheuermann, *Chem. Ber.*, 1967, **100**, 1874; (c) U.S.P. 2,302,162/1942 (*Chem. Abs.*, 1943, **37**, 2016); (d) W. R. Sherman, *J. Org. Chem.*, 1961, **26**, 88; (e) S. L. Shapiro, V. A. Parrino and L. Freedman, *J. Org. Chem.*, 1960, **25**, 384; (f) U.S.P. 2,535,968/1950 (*Chem. Abs.*, 1951, **45**, 4276).

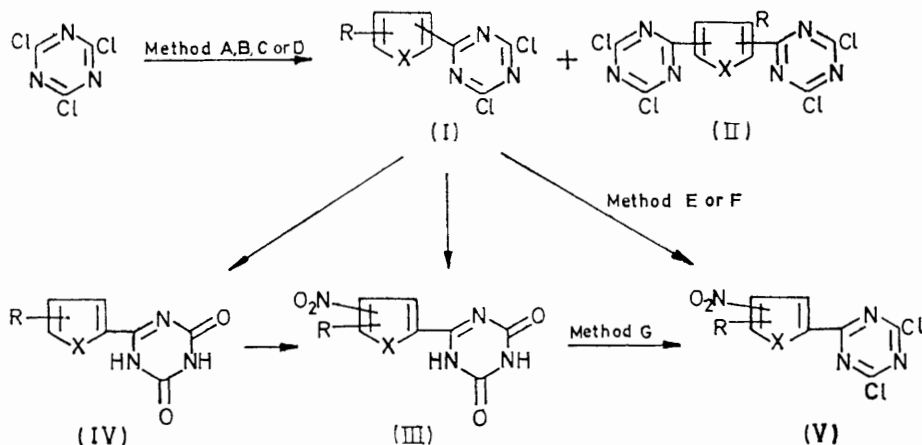
<sup>2</sup> Belg.P. 634,399/1964 (*Chem. Abs.*, 1964, **61**, 671).

<sup>3</sup> (a) R. Hirt, H. Nidecker, and R. Berchtold, *Helv. Chim. Acta*, 1950, **33**, 1365; (b) H. Koopman, *Rec. Trav. chim.*, 1961, **80**, 158.

or pyrrole reacts with cyanuric chloride at low temperature to give the corresponding aryl-dichloro-s-triazine (I). The metallations involved either direct reaction of the aromatic compound with *n*-butyl-lithium (method A), or a halogen-lithium exchange reaction (method B). In certain cases, suitable Grignard reagents were made by treating the aryl halide with

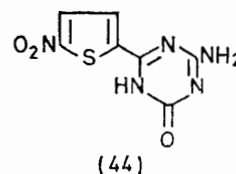
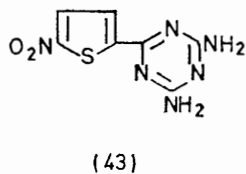
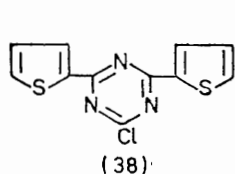
spective metallated species and also by analytical and spectroscopic methods.

With an excess of 2-thienylmagnesium bromide in boiling benzene-ether 2-chloro-4,6-bis-(2-thienyl)-*s*-triazine (38) was obtained. With lithiated 3-methylthiophen substitution occurred in both the 2- and the 5-position, yielding 3-methyl-2-thienyl-*s*-triazine (6) and



(I) <sup>a</sup>	(1)	H	O	(II) <sup>b</sup>	(33)	Me	S	
	(2)	5-Me	O		(34)	H	NEt	
	(4)	H	S		(35)	H	NPr <sup>i</sup>	
	(5)	H	S (3-subst.)		(36)	H	NBu <sup>a</sup>	
	(6)	3-Me	S		(37)	H	NBu <sup>t</sup>	(2,4-disubst.)
	(7)	4-Me	S					
	(8)	5-Et	S					
	(9)	3-MeO	S	(III)	(39)	H	S	4-NO <sub>2</sub>
	(10)	5-MeO	S		(40)	4-Me	S	5-NO <sub>2</sub>
	(11)	5-Br	S		(41)	5-Et	S	4-NO <sub>2</sub>
	(12)	5-Ac	S		(42)	H	NMe	4-NO <sub>2</sub>
	(15)	4,5-Benzo	S					
	(16)	H	NH	(IV)	(45)	H	NH	
	(17)	H	NMe		(46)	H	NMe	
	(18)	H	NEt					
	(19)	H	NPr <sup>i</sup>	(V)	(3)	H	O	5-NO <sub>2</sub>
	(20)	H	NBu <sup>a</sup>		(13)	H	S	4-NO <sub>2</sub>
	(21)	H	NBu <sup>t</sup>		(14)	5-Et	S	4-NO <sub>2</sub>
	(22)	H	N-CH <sub>2</sub> Ph		(25)	H	NH	5-NO <sub>2</sub>
	(23)	5-Me	NH (3-subst.)		(28)	H	NMe	4-NO <sub>2</sub>
	(24)	2,5-Me <sub>2</sub>	NH (3-subst.)		(29)	H	NMe	4,5-(NO <sub>2</sub> ) <sub>2</sub>
	(26)	5-Me	NMe					
	(27)	4,5-Br <sub>2</sub>	NMe					
	(30)	4,5-Benzo	NMe (3-subst.)					
	(31)	Dibenzofuran-4-yl						
	(32)	Dibenzothiophen-4-yl						

<sup>a</sup> Substitution in the 2-position except where noted otherwise. <sup>b</sup> Substitution in the 2- and 5-positions, except where noted otherwise.



Full details of the preparation and physical constants, etc., of compounds (1)–(44) are given in Supplementary Publication no. SUP 20810 (16 pp.) [for details of Supplementary Publications see *J. Chem. Soc. (A)*, 1970, Issue No. 20 (Notice to Authors No. 7)].

magnesium (method C), or by employing the entrainment procedure (method D). The dihalogeno-heteroaryl-*s*-triazines (I) were characterised by analogy with the normal reaction products derived from the re-

4-methyl-2-thienyl-*s*-triazine (7), respectively, the latter being the main product. A minor amount of 3-methyl-2,5-ditriazinylthiophen (33) was also isolated, presumably derived from a dilithiated species (3-methyl-

thiophen is known to undergo monolithiation largely in the 5-position and to some extent in the 2-position<sup>4</sup>).

1-Methylpyrrol-2-yl-lithium gave the desired 2,4-dichloro-6-(1-methylpyrrol-2-yl)-s-triazine (17) in *ca.* 50% yield. This compares favourably with the similar carboxylation, for which a yield of 42% of 1-methylpyrrole-2-carboxylic acid is reported.<sup>5</sup> No other substituted pyrrole was isolated. Lithiation of higher *N*-alkylpyrroles under similar conditions and subsequent coupling with cyanuric chloride afforded mono- (I) as well as di-substituted pyrroles (II), in the molar ratio of *ca.* 2:1 in each case. In the cases of 1-ethyl-, 1-isopropyl-, and 1-butyl-pyrrole, monosubstitution occurred at the 2-position and disubstitution at the 2- and 5-positions. With 1-*t*-butylpyrrole, disubstitution occurred at the 2- and 4-positions instead, presumably owing to a steric factor. The formation of disubstituted pyrroles under these conditions was unexpected, since dilithiation of 1-methylpyrrole is reported to occur only when 3 mol. equiv. of *n*-butyl-lithium are used.<sup>5</sup>

Electrophilic substitution reactions of furan, thiophen, and pyrrole are modified by substituents already present in the ring. With electron-withdrawing substituents such reactions proceed less readily in all three cases and  $\beta$ -substitution may become predominant.<sup>6</sup> With this in mind we have studied the nitration and bromination reactions of the heteroaryl-*s*-triazines, in which the *s*-triazinyl group is a strongly electron-withdrawing  $\alpha$ -substituent. We also hoped that the nitration reactions would provide a synthetic route to nitro-substituted heteroaryl-*s*-triazines, the preparation of which is not normally feasible by the methods described above. The nitration of certain phenyl-*s*-triazines has been reported.<sup>7</sup> Such nitro-derivatives have also been prepared by methods where an aromatic substrate bearing the nitro-substituent is used in the synthesis of the triazine ring.<sup>1a,3b,8</sup> 2,4-Diamino-6-(5-nitro-2-thienyl)-*s*-triazine (43) was prepared by a general route.<sup>1a</sup> In order to obtain the corresponding dihalogeno-*s*-triazine, we needed to hydrolyse this compound (43) to its dioxo-analogue (III; R = H, X = S) prior to halogenation. However, attempted hydrolysis with aqueous 20% hydrochloric acid<sup>9</sup> at 100–105° gave only *ca.* 20% of a monoamino-derivative, as its hydrochloride (44). With strong acids<sup>2</sup> extensive decomposition occurred. The difficulties in hydrolysis of such compounds bearing acid-sensitive heteroaryl systems make this preparative route unsuitable.

Nitration of 2,4-dichloro-6-(2-furyl)-*s*-triazine (1) with mixed acids (concentrated sulphuric acid–nitric acid) gave only the 5-nitro-derivative, with simultaneous hydrolysis of the triazine chloro-substituents; the product was thus the dioxo-derivative (III; R = H,

X = O). 2,4-Dichloro-6-(2-thienyl)-*s*-triazine (4) on similar treatment afforded a mixture of 4- and 5-nitro-derivatives in the molar ratio 4:1, respectively. In an attempt to increase the proportion of 5-nitro-isomer, we found that with a mixture of 70% sulphuric acid and nitric acid 35% of the 5-isomer and 65% of the 4-isomer could be obtained. In all cases, a simultaneous hydrolysis of the chloro-substituents occurred, leading to the respective dioxo-derivatives (III). When the hydrolysed derivative (IV; R = H, X = S) of the dichloro-*s*-triazine (4) was subjected to nitration with the mixed acids, mainly the 4-nitro-derivative (90%) was obtained, the remaining 10% being the 5-isomer. No increase in the proportion of 5-isomer was observed when the dilute acid mixture (70% H<sub>2</sub>SO<sub>4</sub>–HNO<sub>3</sub>) was used. 2,4-Dichloro-6-(pyrrol-2-yl)-*s*-triazine (16), when nitrated with concentrated sulphuric acid–nitric acid, produced *ca.* 95% of the 4-nitropyrrolyl-*s*-triazine, the rest being the 5-isomer; both products were obtained in the dioxo-form (III; R = H, X = NH). The corresponding dioxo-derivative (IV; R = H, X = NH), on nitration with 70% sulphuric acid–nitric acid, gave a mixture of 4- and 5-nitropyrroles in the ratio 3:2, respectively. However, this ratio was reversed in favour of the 5-isomer when the dichloro-*s*-triazine (16) was nitrated with acetyl nitrate. On the other hand, the 4-nitro-isomer was favoured<sup>10c</sup> over the 5-isomer (2:1) when 2,4-dichloro-6-(1-methylpyrrol-2-yl)-*s*-triazine (17) was similarly nitrated with acetyl nitrate. The corresponding dioxo-form (IV; R = H, X = NCH<sub>3</sub>), however, on nitration with 70% sulphuric acid–nitric acid, gave almost exclusively the 4-nitro-derivative (95%). The dichloro-*s*-triazine (17) was also nitrated with concentrated sulphuric acid–nitric acid to give the 4,5-dinitro-derivative (29). Except in the case of this dinitrated product (29), and the nitration of compound (16) with acetyl nitrate, the substitution pattern and isomer distributions were essentially consistent with the previous reports<sup>6,10</sup> of nitration of these five-membered rings carrying an electron-withdrawing  $\alpha$ -substituent. A pronounced 4-directing influence due to the triazinyl group in most cases predominates over the  $\alpha$ -directing effect of the heteroatom of the thiophen or pyrrole ring.

2,4-Dichloro-6-(1-methylpyrrol-2-yl)-*s*-triazine (17), on treatment with 1 equiv. amount of bromine in carbon tetrachloride, produced a mixture of 4- and 5-bromopyrroles in the ratio of 6:1, respectively. From this mixture, the 4-bromo-compound was isolated by crystallisation. G.l.c.–mass spectroscopy showed *ca.* 5% of another component, *M*<sup>+</sup> 352. This suggests that one of the triazine chlorine atoms is replaced by a bromine

<sup>4</sup> V. A. Titkof and I. D. Pletnev, *Zhur. obshchei Khim.*, 1963, **33**, 1983 (*Chem. Abs.*, 1963, **59**, 15408).

<sup>5</sup> V. I. Mur, L. S. Krasnovskaya, and E. A. Masalova, *Zhur. obshchei Khim.*, 1964, **34**, 4125 (*Chem. Abs.*, 1965, **62**, 9132).

<sup>10</sup> (a) W. Seidenfaden and D. Parrellek, in 'Methoden der Organischen Chemie,' ed. E. Muller, Thieme Verlag, Stuttgart, 1971, vol. X/1, p. 690; (b) I. J. Rinkes, *Rec. Trav. chim.*, 1933, **52**, 538; A. H. Blatt, S. Bach, and L. W. Kresch, *J. Org. Chem.*, 1957, **22**, 1693; I. J. Rinkes, *Rec. Trav. chim.*, 1934, **53**, 1167; (c) H. J. Anderson, *Canad. J. Chem.*, 1957, **35**, 21; 1959, **37**, 2053.

<sup>4</sup> V. Ramanathan and R. Levine, *J. Org. Chem.*, 1962, **27**, 1667.

<sup>5</sup> D. A. Shirley, B. H. Gross, and P. A. Roussel, *J. Org. Chem.*, 1955, **20**, 225.

<sup>6</sup> K. J. Morgan and D. P. Morrey, *Tetrahedron*, 1971, **27**, 245.

<sup>7</sup> U.S.P. 2,800,468/1957 (*Chem. Abs.*, 1957, **51**, 18,630).

atom to form 2-bromo-4-[4-(or 5)-bromo-1-methylpyrrol-2-yl]-6-chloro-*s*-triazine. The fact that the intensities of the four peaks corresponding to the molecular ion group at *m/e* 350, 352, 354, and 356, are in close agreement with those expected (3:7:5:1) confirms this assignment. Such a replacement has also been observed during the preparation of monoalkyldichloro-*s*-triazines from cyanuric chloride and alkylmagnesium bromides.<sup>11</sup> A similar reaction with 2 equiv. of bromine, however, gave mainly the 4,5-dibromo-pyrrole, along with some 4-bromo-derivative in the molar ratio 3:1. Other examples of the predominance of 4- over 5-substitution and of the formation of 4,5-dibromopyrroles are known.<sup>12</sup> No substitution on the thiophen or furan ring was observed by n.m.r. methods when the corresponding thienyl-*s*-triazine (4) or furyl-*s*-triazine (1) was subjected to similar bromination conditions.

#### EXPERIMENTAL

Unless otherwise specified, i.r. spectra are quoted for KBr discs, u.v. spectra for solutions in methanol, and n.m.r. spectra for solutions in CDCl<sub>3</sub> (Me<sub>4</sub>Si as internal reference).

**2,4-Dichloro-6-heteroaryl-*s*-triazines (I).** *Methods A, B, C, and D.*—Freshly prepared solutions or suspensions of organo-lithium or Grignard reagents in ether-hexane were added during 1–2 h to a stirred solution of cyanuric chloride in benzene at 5–10°. The mixture was stirred for a further 1 h, then left overnight at room temperature, and evaporated under vacuum. The residue was extracted with ether and the extract was evaporated. The product was purified by crystallisation from hexane, chloroform-hexane, or acetonitrile, or by chromatography on silica gel columns. In certain reactions, more than one product was isolated as a result of alternative positions of lithiation [compounds (6) and (7)], or of dilithiation [compounds (33)–(37)].

The monosubstituted products were readily separated from the less volatile disubstituted compounds by sublimation under vacuum or, in the case of compounds (21) and (37), by crystallisation from *n*-hexane. The two isomers (6) and (7) were separated by fractional crystallisation from carbon tetrachloride-hexane.

**6-Heteroaryl-*s*-triazine-2,4-diones (IV).**—The dichloro-*s*-triazines (I) (0.05 mol) were heated in ethanol (150 ml) and concentrated hydrochloric acid (5 ml) under reflux for 2–4 h. The insoluble dioxo-compounds separated from the reaction mixtures.

**Nitration of 2,4-Dichloro-6-heteroaryl-*s*-triazines (I) and 6-Heteroaryl-*s*-triazine-2,4-diones (IV).**—The dichloro-compound (4) (11.5 g, 0.05 mol) was added in small portions to a stirred mixture of 98% sulphuric acid (40 ml) and nitric acid (*d* 1.42; 10 ml) at 25–35°. The mixture was stirred for 30 min while being heated to 60°, and then cooled and poured on ice. The precipitate was washed with water and dried to give the crude dioxo-compound (III; R = H, X = S) (11.3 g, 94%),  $\delta$  (Me<sub>2</sub>SO) 8.89 (d, H-3) and 9.12 (d, H-5) (*J* 1.4 Hz) (4-nitro-isomer) and 8.13 (s, H-3 and -4) (5-nitro-isomer) in the ratio 4:1. Recrystallisation from dimethylformamide gave the pure 4-nitro-isomer (39).

The ratios of isomers in the crude products from a series of similar nitrations were determined by n.m.r. methods.

**2,4-Dichloro-6-nitroheteroaryl-*s*-triazines (V).**—*Method E.* The dichloro-compound (17) (2.3 g, 0.01 mol) was added in small portions to a stirred mixture of sulphuric acid (16 ml) and nitric acid (*d* 1.42; 4 ml) at 0–5°. The mixture was stirred for a further 20 min without cooling and then poured on ice. The precipitate was recrystallised from chloroform-hexane to give 2,4-dichloro-6-(1-methyl-4,5-dinitropyrrol-2-yl)-*s*-triazine (29).

*Method F.* A cold solution of fuming nitric acid (*d* 1.50; 0.8 g, 0.012 mol) in acetic anhydride (2 ml) was added dropwise to a stirred suspension of the dichloro-compound (16) (2.15 g, 0.01 mol) in acetic anhydride (12.5 ml) at 0–5°. The mixture was stirred at this temperature for 20 min then poured into ice-water and extracted with ether. The extract was washed with ice-water, saturated sodium hydrogen carbonate solution, and water again, dried, and evaporated to give a crude product (V; R = H, X = NH) (1.4 g),  $\nu_{\max}$  3490, 3140, 1520, and 1355 cm<sup>-1</sup>,  $\delta$  7.18 (d) and 7.40 (d) (*J* 4.2 Hz) (5-nitro-isomer) and 7.78 (d) and 8.00 (d) (*J* 1.7 Hz) (4-nitro-isomer) in the ratio 60:40. Recrystallisation from carbon tetrachloride gave the pure 5-nitro-isomer (25).

*Method G.* The 6-nitroheteroaryl-*s*-triazine-2,4-diones (III) were chlorinated as in the following example. The dioxo-compound (39) (4.8 g, 0.02 mol) was heated under reflux with phosphorus pentachloride (9.0 g, 0.044 mol) and phosphoryl chloride (18 g, 0.12 mol) for 5 h. The solution was stirred with ice (200 g) for 1 h, and the solid product was dried (desiccator) and crystallised from chloroform-hexane to give 2,4-dichloro-6-(4-nitro-2-thienyl)-*s*-triazine (13).

**Bromination of 2,4-Dichloro-6-(1-methylpyrrol-2-yl)-*s*-triazine (17).**—A solution of bromine (0.8 g, 0.005 mol) in carbon tetrachloride (20 ml) was added dropwise to a stirred solution of the *N*-methylpyrrolyl compound (17) (1.15 g, 0.005 mole) in carbon tetrachloride (50 ml) containing a crystal of iodine. The mixture was stirred for 2 h at 0–5° and filtered. The filtrate was washed successively with dilute sodium thiosulphate solution, sodium hydrogen carbonate solution, and water, dried, and evaporated to give a yellow solid (1.3 g),  $\delta$  6.93 (d, H-5) and 7.45 (d, H-3) (*J ca.* 2.0 Hz) (4-bromo-isomer) and 6.38 (d, H-4) and 7.50 (d, H-3) (*J ca.* 4.0 Hz) (5-bromo-isomer) in the ratio 6:1. Fractional crystallisation from carbon tetrachloride-hexane gave 2-(4-bromo-1-methylpyrrol-2-yl)-4,6-dichloro-*s*-triazine, m.p. 140–142°,  $\delta$  6.93 (d) and 7.43 (d) (Found: C, 30.0; H, 1.95; N, 16.9. C<sub>8</sub>H<sub>5</sub>BrCl<sub>2</sub>N<sub>4</sub> requires C, 31.1; H, 1.65; N, 18.2%), possibly contaminated with 2-bromo-4[4-(or 5)-bromo-1-methylpyrrol-2-yl]-6-chloro-*s*-triazine.

This reaction was repeated with twice the amount of bromine, giving a crude product,  $\delta$  6.90 (d) and 7.48 (d) (*J ca.* 1.8 Hz) (4-bromo) and 7.60 (s, H-3) (4,5-dibromo) in the ratio 1:3, from which the 2,4-dichloro-6-(4,5-dibromo-1-methylpyrrol-2-yl)-*s*-triazine (27) was isolated by crystallisation from carbon tetrachloride.

**2,4-Diamino-6-(5-nitro-2-thienyl)-*s*-triazine (43).**—A solution of sodium methoxide [from sodium (1.0 g, 0.04 g atom)] in methanol (20 ml) was added to a suspension of biguanide sulphate (6.2 g, 0.02 mol) in methanol (30 ml). Ethyl 5-nitrothiophen-2-carboxylate (4.02 g, 0.02 mol) was added and the mixture was stirred for 48 h. The solid

<sup>11</sup> A. D. Forbes, P. Gould, and I. R. Hills, *J. Chem. Soc.*, 1965, 1113.

<sup>12</sup> H. J. Anderson and S. F. Lee, *Canad. J. Chem.*, 1965, **43**, 409.

which formed on diluting the mixture with water was washed with water and dried under vacuum at 110° to give the *product* (43) (4.8 g), m.p. >300°,  $\nu_{\max}$  3500, 3490, 1550, 1520, and 1330  $\text{cm}^{-1}$ ,  $\lambda_{\max}$  333 nm ( $\log \epsilon$  3.75),  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 7.80 (1H, d), 8.13 (1H, d) ( $J$  4.2 Hz), and 7.00 (4H, s, 2NH<sub>2</sub>) (Found: C, 35.3; H, 2.65; N, 35.1. C<sub>7</sub>H<sub>6</sub>N<sub>6</sub>O<sub>2</sub>S requires C, 35.3; H, 2.55; N, 35.3%).

*Hydrolysis of 2,4-Diamino-6-(5-nitro-2-thienyl)-s-triazine (43).*—A suspension of the diamino-compound (43) (4.5 g) in 20% w/v hydrochloric acid (120 ml) was heated under reflux for 20 h. The solid product was crystallised from methanol to give 4-amino-6-(5-nitro-2-thienyl)-s-triazin-2-

*one hydrochloride (44)* (1.2 g), m.p. >300°,  $\nu_{\max}$  3590, 3400, 3300, 3200—2300, 1760, 1685, 1590, 1520, 1402, 1335, 1310, and 818  $\text{cm}^{-1}$ ,  $\lambda_{\max}$  327 nm ( $\log \epsilon$  4.22),  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 8.2 (s) (Found: C, 30.4; H, 2.0; N, 24.5. C<sub>7</sub>H<sub>5</sub>N<sub>5</sub>O<sub>3</sub>S.HCl requires C, 30.5; H, 2.2; N, 25.3%).

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