Synthesis of a 2-Methyl-4-sulfanilamido-*s*-triazine Derivative (I)

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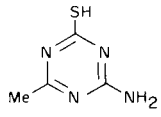
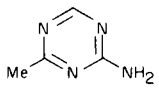
An attempt to obtain 2-methyl-4-sulfanilamido-*s*-triazine (XXI) by condensation of 2-amino-4-methyl-*s*-triazine (II) with *p*-acetamidobenzenesulfonyl chloride (III) in pyridine and in benzene containing trimethylamine gave instead the unexpected products, guanidine *N*-acetylsulfanilate (IV) (after hydrolysis) and N^1,N^1-dimethylsulfanilamide (V), respectively. On the other hand, 2-methyl-4-methylthio-6-sulfanilamido-*s*-triazine (XIX) was obtained from 4,6-dimethylthio-*s*-triazine (XVII), but the reduction of XIX with Raney nickel in aqueous sodium hydroxide solution also gave an unexpected compound, sulfaguanidine (XX).

In continuation of the studies on the synthesis and chemotherapy of sulfa drugs (3), preparation of 2-methyl-4-sulfanilamido-*s*-triazine (XXI) was attempted using two different methods to give the abnormal guanidinium salt (IV) and the triazine derivative (XIX), the structures of which are reported in this paper.

CHART I



I



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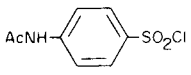

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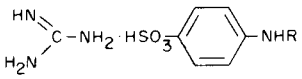
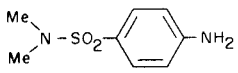
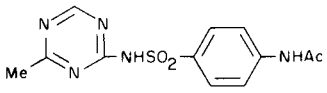


IV, R = Ac
IVa, R = H



V

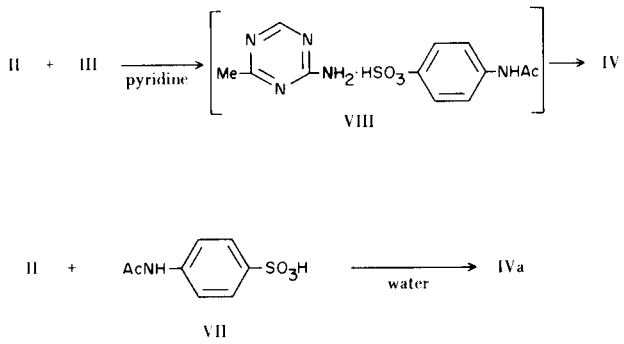


VI

Firstly, 2-amino-4-methyl-*s*-triazine (II), prepared by reduction of 2-amino-4-mercapto-6-methyl-*s*-triazine (I) (4) over Raney nickel in aqueous sodium hydroxide solution, was condensed with *p*-acetamidobenzenesulfonyl chloride (III) in pyridine as usual to give an unexpected product (IV), the ir spectrum (potassium bromide) of which showed strong absorptions at 1660 (amide C=O), 1324 and 1170 cm^{-1} (SO_2), and its nmr spectrum (δ) in deuteriodimethylsulfoxide revealed the methyl protons of the acetyl group at 2.06 as a singlet together with four aromatic protons due to the phenyl group. The signals at 7.05 (6H, broad) and 10.01 (1H), which disappeared by addition of deuterium oxide, were assigned to the amino and imino protons of NH_2-$\overset{\overset{NH}{\|}}{C}$-$\overset{+}{N}H_3$ and amidocarbonyl protons of CONH group, respectively. These facts and its microanalysis supported the structure of guanidinium *N*-acetylsulfanilate (IV), which was identical with an authentic sample prepared by Protiva (5) by the mixed melting point test. However, hydrolysis of II with pyridine for 1 hour at 95° was not effected and, moreover the reaction of II with VII in dry pyridine or in water at room temperature for 20 hours under stirring recovered both starting materials. On the other hand, when a mixture of II and VII were refluxed in water, guanidine sulfanilate (IVa) was obtained. Therefore the salt (IV) would be presumably formed by hydrolysis of II and III, followed by salt formation, during the course of the reaction, but not post-treatment.

In order to examine the reactivity of II, acetylation of II with acetic anhydride was carried out for 2.5 hours at 85° to give 2-acetamido-4-methyl-*s*-triazine (IX). When the above reaction was done at reflux and the mixture

CHART 2



quenched in water, it afforded the unexpected product monoacetylguanidine acetate (XII), which was identical with an authentic sample (6).

A mechanism which would explain the formation of XII involves the initial ring opening of the acetyl compound (IX), followed by hydrolysis, to give XII.

Treatment of II with hydrogen chloride in methanol afforded the hydrochloride of II, whereas heating with 10% hydrochloric acid converted it to acetylguanidine (XI) (7) which when isolated and treated with moist ethyl acetate gave XII.

CHART 3

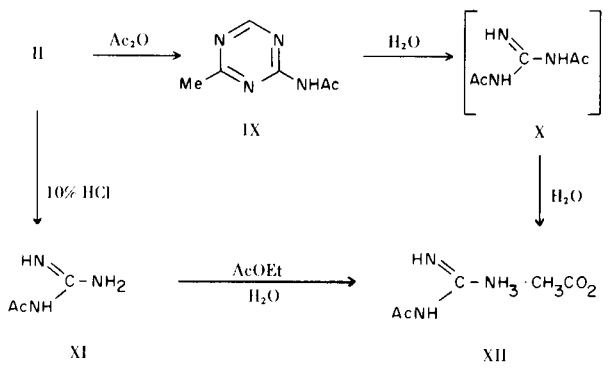
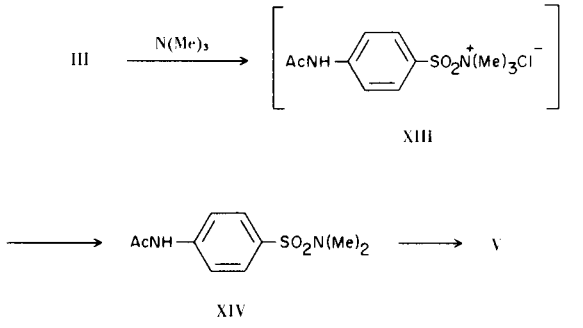


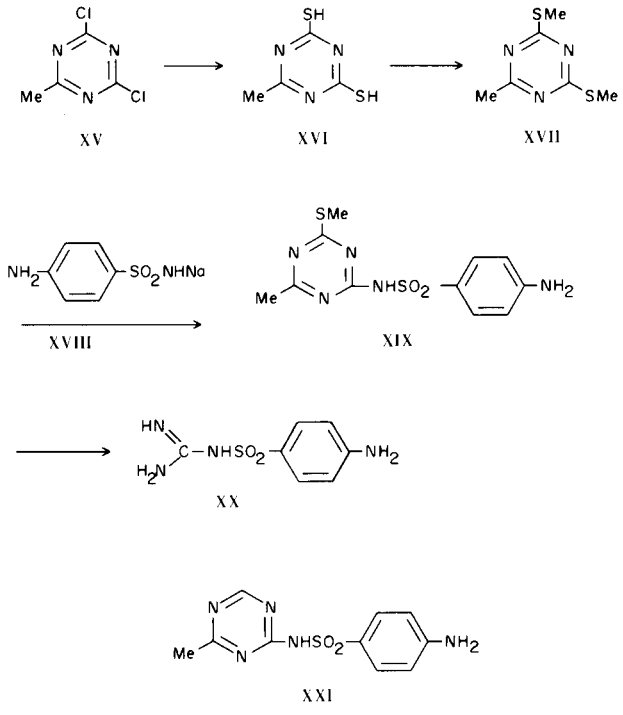
CHART 4



Furthermore, heating of II with 30% aqueous sodium hydroxide solution for 1 hour at 160-170° in a sealed tube afforded a dark brown resinous product, the structure of which remained unclear. On the other hand, the reaction of II with III in benzene containing trimethylamine gave instead, the abnormal product, N^1,N^1-dimethylsulfanilamide (V) was obtained after alkaline hydrolysis, the structure of which was identical with a sample prepared by Walker (8) by the mixed melting point test. This compound would be formed *via* an intermediate (XIII) (9).

Since the condensation of II with III did not give the expected product (VI), its synthesis by reduction of 2-methyl-4-methylthio-6-sulfanilamido-*s*-triazine (XIX) was examined as follows. Methylation of 2-methyl-4,6-dimercapto-*s*-triazine (XVI), which was obtained from 3,4-dichloro-6-methyl-*s*-triazine (XV) (9), with methyl iodide in aqueous sodium hydroxide solution gave 2-methyl-4,6-dimethylthio-*s*-triazine (XVII). Condensation of XVII with sodium sulfanilamide (XVIII) in dimethylformamide afforded an expected product, the sulfanilamido-*s*-triazine (XIX), the structure of which was determined in the following way. The molecular formula, $C_{11}H_{13}N_5O_2S_2$, was supported by microanalysis and mass spectrometry (M^+ 311), and the ir spectrum (potassium bromide) showed strong absorptions at 3300, 3200, and 1150 cm^{-1}. Furthermore, the nmr spectrum supports the structure of the sulfanilamide (XIX) as described in the experimental section.

CHART 5



Reduction of XIX with Raney nickel in aqueous sodium hydroxide solution gave an unexpected compound (XX) as the main product, the spectral data of which were superimposable upon those of an authentic sample (XX) prepared by Winnek (12). This reaction was examined under various conditions, but the expected compound (XXI) was not obtained. Further studies on the synthesis of XXI are in progress.

EXPERIMENTAL

All melting points were determined on a Yanagimoto Micro melting point apparatus and are uncorrected. Infrared spectra were measured with a Hitachi EPI-2 spectrophotometer and partly with a Hitachi grating ir spectrophotometer Model EPI-G3, and nmr spectra were taken with a Hitachi Perkin-Elmer R-20A spectrometer using tetramethylsilane as an internal standard. The mass spectra were determined with a Hitachi RMU-7E spectrometer.

2-Amino-4-methyl-*s*-triazine (II).

A mixture of 28 g. of 2-amino-4-mercapto-6-methyl-*s*-triazine (I) (4), 150 ml. of 30% ammonia, 100 ml. of water and 44 g. of Raney nickel was heated under reflux for 2 hours. After the removal of inorganic material by filtration, the filtrate was allowed to stand at room temperature overnight. The crystals which separated were removed and the filtrate was evaporated under reduced pressure to give a solid, which was recrystallized from water to give 9.8 g. (45%) of II as colorless needles, m.p. 187-188°; nmr (trifluoroacetic acid) δ: 2.86 (3H, singlet, CH_3), 8.5 (2H, broad singlet, NH_2); (deuteriodimethylsulfoxide) δ: 2.31 (3H, singlet, CH_3), 7.45 (2H, broad singlet, NH_2), 8.42 (1H, singlet, C_6-*H*).

Anal. Calcd. for $C_4H_6N_4$: C, 43.63; H, 5.49; N, 50.88. Found: C, 43.66; H, 5.43; N, 50.76.

Hydrochloride: colorless needles, m.p. 207-208° (from methanol-ether).

Anal. Calcd. for $C_4H_6N_4 \cdot HCl$: C, 32.78; H, 4.81; N, 38.22. Found: C, 32.91; H, 4.89; N, 38.35.

Reaction of 2-Amino-4-methyl-*s*-triazine (II) with *p*-Acetamidobenzenesulfonyl Chloride (III).

(a) A suspension of 1.1 g. (10 mmoles) of II and 2.4 g. (10 mmoles) of III in 20 ml. of dry pyridine was stirred at room temperature for 20 hours. After the recovery of starting material (II) by filtration, the reddish-brown filtrate was evaporated below 40° under reduced pressure to give a reddish viscous syrup, which was dissolved in 5 ml. of water and allowed to stand. The crystals which separated were collected by filtration, washed with water and dried to give the crude product (IV), which was recrystallized from water to afford 0.3 g. of guanidine *N*-acetylsulfanilate (IV) as pale yellow needles, m.p. 310° [lit. (5), m.p. 310°], identical with the sample prepared by Protiva (5) by the mixed m.p., ir (potassium bromide), nmr and tlc.

(b) To a stirred mixture of 1.1 g. of II, 2.4 g. of III, and 20 ml. of dry methylene chloride was added a solution of 1.2 g. of trimethylamine in 10 ml. of dry benzene during 20 minutes below 50° and the stirring was continued further for 4 hours at 40-50°, and then allowed to stand at room temperature overnight. The resulting solution was concentrated under reduced pressure and the residue was dissolved in 20 ml. of 10% sodium hydroxide, then heated on a water-bath for 1.5 hours. After cooling, the crystals which separated were collected by filtration, washed with water and dried to give 0.8 g. of N^1,N^1-dimethylsulfanilamide (V), the recrystallization of which from methanol gave colorless needles, m.p. 169-170° [lit. (8), m.p. 169-170°], identical with the authentic sample (8).

Reaction of II with Acetic Anhydride.

(a) A stirred solution of 1 g. of II in 20 ml. of acetic anhydride was heated on a water-bath for 2.5 hours at 85°. After cooling, the precipitated crystals were collected by filtration. Recrystallization from benzene gave 2-acetamino-4-methyl-*s*-triazine (IX) as colorless needles, m.p. 133°; ir ν max (potassium bromide) cm^{-1}: 3180 (amide NH), 1710 (C=O); nmr (deuteriodimethylsulfoxide) δ: 2.65 and 2.60 (each 3H, each singlet, $COCH_3$ and CH_3), 8.90 (1H, singlet, C_6-*H*), 9.45 (1H, broad singlet, N*H*).

Anal. Calcd. for $C_6H_8N_4O$: C, 47.36; H, 5.30; N, 36.82. Found: C, 47.56; H, 5.40; N, 36.98.

(b) A solution of 1 g. of II in 10 ml. of acetic anhydride was heated under reflux for 10 minutes. After cooling, the reaction mixture was poured into ice-water and the resulting aqueous solution was concentrated under reduced pressure. The residue was recrystallized from methanol to give 0.7 g. of monoacetylguanidine acetate (XII) as colorless needles, m.p. 176-178° [lit. (6), m.p. 176-178°], identical with the authentic sample prepared by Ryabinin (6).

Hydrolysis of II with Hydrochloric Acid.

A solution of 1 g. of II in 10 ml. of 10% hydrochloric acid was heated on a water-bath for 1 hour. After cooling, the resulting solution was basified with 10% ammonia and concentrated under reduced pressure to give monoacetylguanidine (XI) as a colorless viscous syrup (13), which was dissolved in moist ethyl acetate and then allowed to stand in a refrigerator for 5 days. The separated crystals were collected by filtration and recrystallized from methanol to give 0.3 g. of the salt, which was identical with XII (6) by the mixed m.p., ir and tlc.

2-Methyl-4,6-dimethylthio-*s*-triazine (XVII).

To a solution of 3 g. of metallic sodium in 60 ml. of dry methanol saturated with dry hydrogen disulfide was added 10 g. of 2,4-dichloro-6-methyl-*s*-triazine (XV) (10) under cooling during 20 minutes and the reaction mixture was allowed to stand overnight to separate crystals. The crystals were collected by filtration, washed with water, and dried to give 6 g. of 2,4-dimercapto-6-methyl-*s*-triazine (XVI) as a colorless powder, m.p. $> 300°$, which was used in the following reaction without purification.

A mixture of 3.2 g. of the above dithiol (XVI), 20 ml. of 10% sodium hydroxide, and 5.6 g. of methyl iodide was shaken for 1 hour at room temperature. The crystals which separated were collected by filtration, washed with water and dried to give 3.2 g. of XVII, which was recrystallized from methanol to give 3 g. of colorless needles, m.p. 76-77°.

Anal. Calcd. for $C_6H_9N_3S_2$: C, 38.48; H, 4.84; N, 22.44. Found: C, 38.74; H, 5.13; N, 22.03.

2-Methyl-4-methylthio-6-sulfanilamido-*s*-triazine (XIX).

A mixture of 1.8 g. of XVII, 1.9 g. of sodium sulfanilamide (XVIII), and 20 ml. of dimethylformamide was heated on a water-bath for 7 hour inspecting with tlc. The reaction mixture was concentrated under reduced pressure, and the residue was triturated with water and the insoluble material (XVII) was removed by filtration. The filtrate was adjusted to *p*H 5 with 10%

hydrochloric acid, and the precipitate was recrystallized from methanol to give 0.6 g. of XIX as colorless needles, m.p. 92-93° dec.; ir ν max (potassium bromide) cm^{-1}: 3300, 3200 (NH_2), 1150 (SO_2); nmr (deuteriodimethylsulfoxide) δ: 2.33 and 2.45 (each 3H, each singlet, CH_3 and SCH_3), 6.6 and 7.6 (each 2H, each doublet, J = 9 Hz, aromatic protons). Mass m/e: 311 (M^+).

Anal. Calcd. for $C_{11}H_{13}N_5O_2S_2$: N, 22.49. Found: N, 22.47.

Reduction of XIX.

A mixture of 6.4 g. of XIX, 45 g. of Raney nickel, 20 ml. of 28% ammonia and 200 ml. of water was heated under reflux for 2 hours. The reaction mixture was filtered and the filtrate was concentrated to dryness. The residue was triturated with 30 ml. of 2% sodium hydroxide at room temperature to give 0.9 g. of sulfaguanidine (XX) as colorless needles, m.p. 190-192° [lit. (12), m.p. 190-193°], which was identical with an authentic sample (12) by the mixed m.p. and ir spectral comparison.

The Reaction of II with VII in Water.

A stirred mixture of 0.6 g. of II, 1.1 g. of VII, and 20 ml. of water was refluxed for 3 hours and the reaction mixture was evaporated under reduced pressure to give a solid, which was admixed with 3 ml. of water. The crystals were collected and recrystallized from water to give IVa as a powder, m.p. 264-266°; ir ν max (potassium bromide) cm^{-1}: 2800-3400 cm^{-1} (absorption due to ammonium salt).

Anal. Calcd. for $C_7H_{12}N_4O_3S$: C, 36.19; H, 5.21. Found: C, 36.46; H, 4.83.

In the above reaction starting materials were recovered quantitatively after stirring at room temperature for 20 hours.

Acknowledgments.

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(2) Communications concerning this paper should be directed to Professor Tetsuji Kametani.

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(13) The picrate, yellow needles (from ethanol) m.p. 300° [lit. (7), m.p. 300°].