3-Monosubstituted and 3,6-Unsymmetrically Disubstituted 1,2,4,5-Tetrazines. A General Method of Synthesis

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A stepwise procedure has been developed for the synthesis of 3,6-unsymmetrically disubstituted- or 3-monosubstituted-1,2,4,5-tetrazines, based upon the facile substitution either of an alkylthio group in 3,6-bis(alkylthio)-1,2,4,5-tetrazines (**1**) and (**2**) by nitrogen nucleophiles, particularly by hydrazine, or of a bromo group, obtained by oxidation of a hydrazino group or by an independent synthesis, by carbon nucleophiles. The ultraviolet-visible spectra and some nuclear magnetic resonance properties are discussed.

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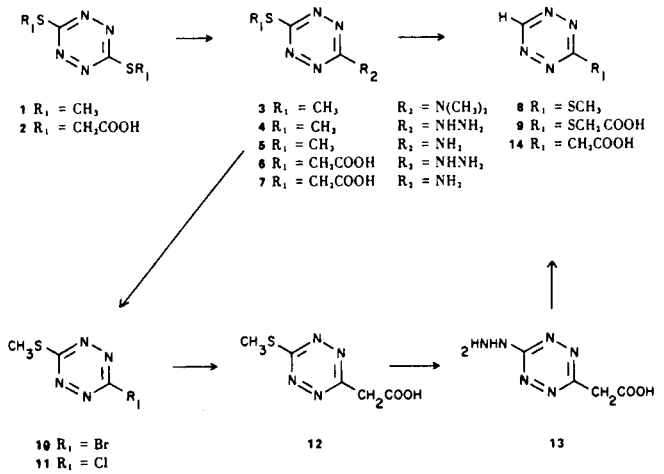
By the nucleophilic attack of hydrazine on nitriles (1,2), imidates (3), amidines (4), thioamides (5), and aldehydes (6) symmetrical 3,6-disubstituted 1,2,4,5-tetrazines (7a-b) are easily prepared, while unsymmetrically 3,6-disubstituted 1,2,4,5-tetrazines are much more difficult to synthesize and only a few of these compounds are reported in the literature, following either the preceding routes (4,6,8) or "nonconventional" procedures (9-10). We now report a general stepwise method to prepare 3,6-unsymmetrically disubstituted or 3-monosubstituted 1,2,-4,5-tetrazines in yields of preparative interest. Particularly, our main goal was the synthesis of the acids **9**, **14**, **18** and **19**, as intermediates for "semisynthetic" β-lactam antibiotics (11).

Synthesis.

The known (12) nucleophilic substitution of a methylthio group in 3,6-dimethylthio-1,2,4,5-tetrazine (**1**) by dimethylamine giving **3** prompted us to investigate the reaction of **1** and of 3,6-bis(carboxymethylthio)-1,2,4,5-tetrazine (**2**) with other nucleophiles. The compounds **1** and **2** were prepared according to the procedure of Sandstrom (13), starting from the readily available thiocarbohydrazide (14) and bis(carboxymethyl)trithiocarbonate (15). The reaction of hydrazine hydrate and ammonia with **1** and **2** at room temperature (Scheme I) gave rise to compounds **4-7**, in fair to good yields. The acids **6** and **7** were isolated as salts with a molecule of hydrazine and ammonia respectively, as evidenced by nmr spectra and analysis. Attempts of direct substitution in **1** and **2** by other nucleophiles, as bromide or the sodium salt of diethylmalonate, were unsuccessful. By the well known reactivity of the amino- and hydrazino-group, it was possible the synthesis of several other derivatives, the hydrazino group being the preferred one owing to the mild oxidative conditions, to which 1,2,4,5-tetrazines are stable (7), during its substitution.

Scheme I

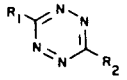


The replacement of the hydrazino group in **4** by hydrogen yielding **8** was obtained by reflux in ethanol in the presence of yellow mercuric oxide, according to the procedure of Lee and Paudler (16) for 1,2,4-triazines, but was better achieved at room temperature using copper sulphate as oxidant in water, in which **4** was dissolved by the addition of sulfuric acid. The hydrazino acids **6** and **13**, soluble in water being isolated as hydrazinium salts, gave rise in the same way to **9** and **14**, respectively, in fair yields. While the methylthio derivative **8** has a high volatility, as already reported in similar 1,2,4,5-tetrazines (4,6,7a), being partially lost during the distillation of ether in which it was extracted, the acids **9** and **14** are stable solids, which furthermore decarboxilate only at very slow rate in organic solution at room temperature. Compounds **8**,**9** and **14** represent the first known examples of 1,2,4,5-tetrazines monosubstituted by aliphatic groups.

The hydrazino acid **13** was synthesized by a multistep sequence starting from **4**. According to the method of Albert and Catterall (17), if the oxidation of the hydrazino group was carried out in the presence of halide ions, it was replaced, affording **10** and **11**, by halogen atoms. They can be easily substituted by nucleophilic reagents, as already reported (10) for the nitrogen ones in similar compounds, *e.g.*, in 3-bromo-6-phenyl-1,2,4,5-tetrazine (**15**). We wanted instead to experiment on **10** the substitution of bromine, which in preliminary tests was shown to be a better leaving group than chlorine in **11**, by a carbon nucleophile, namely with derivatives of malonic acid, to synthesize the corresponding acetic acids. The acid **12** was in fact obtained by reaction of

Table I

Physical and Analytical Data for Compounds

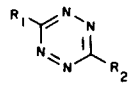


No.	R_1	R_2	M.p. °C	Solvent (a)	Yield % (b)	Formula	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found	% Nitrogen Calcd.	% Nitrogen Found
4	CH_3S	$NHNH_2$	136-138	E	71	$C_3H_6N_6S$	22.78	22.84	3.82	3.83	53.13	53.19
5	CH_3S	NH_2	143-146	E	70	$C_3H_5N_5S$	25.17	25.22	3.52	3.51	48.92	49.14
6	NH_2NH	SCH_2COOH	(c)		87 (d)	(c)						
7	NH_2	SCH_2COOH	156-158	ET	55 (d)	(e)						
8	H	SCH_3	29-30	ET-LP	35	$C_3H_4N_4S$	28.12	28.22	3.15	3.14	43.72	43.80
9	H	SCH_2COOH	124-125	ET	52	$C_4H_4N_4O_2S$	27.90	27.84	2.34	2.35	32.54	32.69
10	CH_3S	Br	(f)		59	$C_3H_3BrN_4S$	17.40	17.43	1.46	1.46	27.06	27.12
11	CH_3S	Cl	31-33	LP	75	$C_3H_3ClN_4S$	22.16	22.30	1.86	1.85	34.46	34.61
12	CH_3S	CH_2COOH	96	ET-LP	31	$C_5H_6N_4O_2S$	32.25	32.36	3.25	3.24	30.09	29.99
13	NH_2NH	CH_2COOH	(g)		79 (d)	(g)						
14	H	CH_2COOH	89	ET-LP	40	$C_4H_4N_4O_2$	34.29	34.23	2.88	2.89	39.99	39.77
16	C_6H_5	$CH(COOC_2H_5)_2$	63-65	LP	69	$C_{15}H_{16}N_4O_4$	56.96	56.79	5.10	5.11	17.71	17.64
17	C_6H_5	OC_2H_5	103-105	LP	21	$C_{10}H_{10}N_4O$	59.40	59.10	4.98	5.01	27.71	27.60
18	C_6H_5	SCH_2COOH	160-162	C	68	$C_{10}H_8N_4O_2S$	48.38	48.17	3.25	3.26	22.57	22.59
19	C_6H_5	CH_2COOH	139-140	B	83	$C_{10}H_8N_4O_2$	55.55	55.60	3.73	3.74	25.91	25.76
21	C_6H_5	CH_3	70-72	LP	75	$C_9H_8N_4$	62.78	63.01	4.68	4.67	32.54	32.47

(a) Solvent of crystallization; E, ethanol; ET, diethyl ether; LP, light petroleum (b.p. 30-50°); B, benzene. (b) No attempts were made to optimize yields. (c) Characterized as hydrazinium salt, m.p. 118-123° from ethanol. *Anal.* Calcd. for $C_4H_{10}N_8O_2S$: C, 20.50; H, 4.30; N, 47.84. Found: C, 20.53; H, 4.31; N, 47.90. (d) Yield calculated on the corresponding salt (of hydrazine or ammonia). (e) Characterized as ammonium salt, m.p. 168-170° from ethanol. *Anal.* Calcd. for $C_4H_8N_6O_2S$: C, 23.52; H, 3.95; N, 41.15. Found: C, 23.50; H, 3.90; N, 41.00. (f) The compound was an oil, which was purified by column chromatography (see Experimental). (g) Characterized as hydrazinium salt, m.p. 136-139° from ethanol. *Anal.* Calcd. for $C_4H_{10}H_8O_2$: C, 23.76; H, 4.98; N, 55.43. Found: C, 23.65; H, 4.98; N, 55.10.

Table II

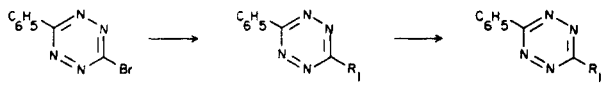
Nmr and Electronic Absorption Data for Compounds



No.	R_1	R_2	Solvent	Nmr Data, Chemical Shifts in δ (a) R_1'	R_2	Visible and Uv Data λ			ε	
3	CH_3S	$N(CH_3)_2$	$CDCl_3$	2.66	3.33	*510*	458	276	784	1168	23843
4	CH_3S	$NHNH_2$	DMSO-d_6	2.62	4.5 (br, NH_2), 9.3 (br, *NH*)	*500*	442	268	601	936	19142
5	CH_3S	NH_2	DMSO-d_6	2.60	7.58 br	518	431	263	517	1399	20883
6	$NHNH_2$	SCH_2COOH	DMSO-d_6	6.46 br (c)	3.8	*487* (d)	442	270	714	811	14748
7	NH_2	SCH_2COOH	DMSO-d_6	7.68 br	3.99	516 (e)	416	264	484	1358	18979
8	H	SCH_3	$CDCl_3$	9.96	2.76	525	364	262	407	610	10890
9	H	SCH_2COOH	DMSO-d_6	10.38	4.21	523	355	260	454	681	11350
10	CH_3S	Br	$CDCl_3$	2.8		519	384	271	484	673	17949
12	CH_3S	CH_2COOH	$CDCl_3$	2.7	4.34 (CH_2), 8.35 (br, *OH*)	527	373	263	362	615	11563
13	$NHNH_2$	CH_2COOH	DMSO-d_6	5.4 br (c)	3.72	(f)					
14	H	CH_2COOH	$CDCl_3$	10.8	4.45	539		262	506		2795
16	C_6H_5	$CH(COOC_2H_5)_2$	$CDCl_3$	7.52-7.67 m	1.3 (t, CH_3) (g), 4.32 (q, CH_2), 5.48 (*CH*)	533		266	425		21086
17	C_6H_5	OC_2H_5	$CDCl_3$	7.50-7.67 m	1.6 (t, CH_3) (g), 4.75 (q, CH_2)	(f)					
18	C_6H_5	SCH_2COOH	DMSO-d_6	7.55-7.80 m	4.3	532	376	298	453	982	26768
19	C_6H_5	CH_2COOH	DMSO-d_6	7.57-7.81 m	4.42	537		262	432		23263
20	C_6H_5	OH	DMSO-d	7.30-8.16 m	13 (br, *NH*)	543 (h)	383	272	297	1337	22617
21	C_6H_5	CH_3	$CDCl_3$	7.50-7.70 m	3.08	(f)					
22	C_6H_5 (i)	$NHNH_2$	DMSO-d_6	7.30-8.20 m	4.6 (br, NH_2), 9.7 (*NH*)	525	401	282	508	1166	24481

(a) Singlet if not otherwise stated; br = broad; m = multiplet; t = triplet; q = quartet. (b) In 95% ethanol as solvent; figures in italics denote shoulders. (c) Hydrazine salt. (d) In water. (e) For the ammonium salt the values are: λ, 498, 430, 265; ε, 535, 1162, 16515 in water. (f) Not effected. (g) J = 7 Hz. (h) From reference (10): λ, 545 nm; ε, 317. (i) Synthetized according to reference (10) for comparison.

Scheme II



15 16 R_1 = $CH(COOC_2H_5)_2$ 17 R_1 = OC_2H_5 18 R_1 = SCH_2COOH 19 R_1 = CH_2COOH 20 R_1 = OH

10 with the sodium salt of bis(trimethylsilyl)malonate in apolar solvent; by consequent work-up of the reaction mixture with water, there was an immediate monodecarboxylation following the hydrolysis of the silyl group. The methylthio group in 12 was again weakened (18) and was substituted at room temperature by hydrazine hydrate affording 13, from which 14 was prepared as before reported.

By this sequence of reactions, both the methylthio groups in 1 can be replaced by new substituents, in the mildest conditions as possible, and by the alternate reaction on the hydrazino or halogen groups many 3,6-unsymmetrically disubstituted 1,2,4,5-tetrazines could be obtained.

Other 3,6-unsymmetrically disubstituted 1,2,4,5-tetrazines, with a phenyl substituent as a constant, were prepared (Scheme II) starting from 15 (10), on which we determined furthermore the proper conditions for the nucleophilic substitution of the bromo group with carbon derivatives. The compound 15 was allowed to react with the sodium salt of diethylmalonate, used as a rule (19a-b) for this replacement, giving rise to 16 and/or 17 depending from the solvent in which the reaction was performed. In an aprotic solvent, such as benzene, the diester 16 was obtained in high yields using the salt of diethyl malonate either prepared before or made *in situ*, while 17 was the main product in ethanol, although in low yields. Compound 17 was later synthesized in high yields by reacting 15 with sodium ethoxide in benzene suspension. Our attempts to prepare 19 by hydrolysis of 16 gave no result in acidic conditions, as hydrochloric acid in acetone or dioxane, acetic acid alone or with phosphoric acid, formic acid, methanesulfonic acid in 90% formic acid (20), always recovering the starting product, whereas 20 (10) was obtained using the equimolar quantity of sodium hydroxide in water-methanol, 16 not reacting with a milder base. Therefore, needing a weaker diester of malonic acid, we prepared the bis(trimethylsilyl) derivative, being well known (21) the facility of hydrolysis of the trimethylsilyl group, and without its intermediate isolation, it was allowed to react first with sodium hydride in benzene, giving the corresponding salt, then with 15, affording 19 after hydrolysis and concomitant monodecarboxylation at room temperature in high yields.

The carboxylic group of 19 was lost only at temperature of about 130°, at 20 mm, affording 21, showing again the high stability of these heterocyclic acetic acids. Compound 18 was finally synthesized reacting 15 with mercaptoacetic acid in chloroform solution. The physical and analytical data of compounds 3-21 are summarized in Tables I and II.

Physical Properties.

Besides the two maxima described theoretically (22a-b) at about 540 and 250 nm, the electronic spectra of the unsymmetrically 3,6-disubstituted 1,2,4,5-tetrazines here prepared show a further maximum, formerly observed by Sandstrom (13) in 1 and 2 at 410 nm, the position of this band depending strictly from the substituents. It undergoes a bathochromic shift from 410 nm to 420-460 nm in the presence of a strong electron-donating substituent besides an alkylthio group (Table II, compounds 3-7), an hypsochromic shift to 380-370 nm with a less effective electron-donating group (10,12,18) and to about 360 nm with the monosubstituted compounds 8 and 9. This maximum does not appear in the absence of an electron-donating group (14,16,19, see also reference (6).

The structure of potentially tautomeric 1,2,4,5-tetrazines, such as amino (5,7), hydrazino (4,6,13), and hydroxy derivatives (20) was also determined by physical methods. In 5 and 7 the amino form is more favoured than the corresponding imino form, as already well documented for *N*-heteroaromatic amines (23); in fact their nmr spectra in DMSO-d_6 solution show singlets, slightly broadened, of intensity two, at 7.58 and 7.68 δ, respectively, values which are comparable with the resonances of the amino group in the same solvent at 7.56-6.65 δ for some 3-amino-1,2,4-triazines (24) and at 8.02 δ for 2-aminopyrimidine (25); for this latter compound the aminosignal was at 5.72 δ (26) *vs.* 5.5 δ for 5 in deuteriochloroform solution. In the infrared spectrum of 5, we found bands at 3320 and 3200 cm^{-1}, in potassium bromide disk, and 3530 and 3420 cm^{-1}, in chloroform solution, due to antisymmetric and symmetric stretching vibration of the primary amino group (27). Furthermore, the electronic spectra of 5 and 7 resemble closely that of dimethylamino analogue 3.

The hydrazine structure predominates also in hydrazino compounds as confirmed by ir and nmr spectra. In fact the NH vibrations for 4 at 3300, 3250, 3010 and 1640 cm^{-1} compare well with 3320, 3220, 3070 and 1620 cm^{-1} for phenylhydrazine, in potassium bromide disk. In the nmr spectra of 4 and 22 (28) the resonances (see Table II) for the hydrogens bonded to different nitrogens agree with those in *p*-nitro and 2,4-dinitrophenylhydrazine, in DMSO-d_6 solution, namely 4.4 and 4.9 δ for amino group and 8.3 and 9.75 δ for the NH group respectively, the latter peaks being more influenced by the different electronegativity of the ring. In compound 20 the oxo structure is instead predominant, as shown by ν C=O at

1700 and 1720 cm^{-1}, potassium bromide disk and dioxane solution respectively, and by the NH resonance at 13 δ in the nmr spectra.

Finally the value of 10.48 δ for CH protons in 1,2,4,5-tetrazine, which has been empirically calculated by Nicholson (29), agree well with values found for the three monosubstituted 1,2,4,5-tetrazines synthetized. Further work in this field is now in progress.

EXPERIMENTAL

Melting points were determined in a Kofler type apparatus (Reichert, Austria) and are uncorrected. The nmr spectra were obtained on a Varian T-60A or A-60 spectrometers and ultraviolet-visible spectra were recorded on a Beckmann BB-G spectrophotometer. The infrared spectra were obtained on Perkin-Elmer 257 and 577 instruments using potassium bromide disk, unless otherwise stated. "Silica gel" refers to Kieselgel 60 (70-230 mesh) from Merck, Germany. Thin layer chromatography (tlc) was carried out on precoated silica gel plates (Merck, F-254). Organic solutions were dried on anhydrous sodium sulphate and evaporated under reduced pressure on a rotatory evaporator (Ascenso, Milan, Italy). Compounds **1** and **2** were prepared according to Sandstrom (13) with average total yields of 34 and 37%, respectively, from thiocarbohydrazide, up to 1 mole scale. Compounds **15** and **22** were obtained following reference (10).

3-Hydrazino-6-(methylthio)-1,2,4,5-tetrazine (**4**).

To a stirred mixture of 50 g. (0.287 mole) of **1** in ethanol (2.5 l.) was added dropwise at room temperature a solution of 16.2 g. (0.324 mole) of hydrazine hydrate in ethanol (50 ml.); at the end of the addition all the solid was dissolved. Half an hour later **4** began to precipitate and after 3 hours the solid was filtered, whereas the filtrate was concentrated *in vacuo* to half its volume affording a second crop of precipitate. After another concentration, the mixture was allowed to stand in the refrigerator and a third fraction of solid was filtered. The three crops, 13.7, 15.2, and 3.5 g. (71%) respectively, were mixed together, after checking their purity on tlc (chloroform 20-methanol 1). A sample was crystallized from ethanol, m.p. 136-138°, red plates; ir: 3300, 3250, 3010, 1640, 1530, 1200, 1045, 980 cm^{-1}.

3-Amino-6-(methylthio)-1,2,4,5-tetrazine (**5**).

To a stirred suspension of 0.97 g. (0.0055 mole) of **1** in methanol (25 ml.) was added dropwise a solution of ammonia (5.5 mmoles/ml.) in methanol (3 ml.) at room temperature. When all the solid was dissolved one hour later, the reaction was complete as shown by tlc (benzene 34-ethylacetate 15-acetic acid 1). The solution was evaporated to dryness *in vacuo* and the orange solid was crystallized from ethanol to give 0.55 g. (70%) of **5**, m.p. 143-146°; ir: 3320, 3200, 1640, 1610, 1190, 1050, 980, 920 cm^{-1}.

In the same way, 3-(dimethylamino)-6-(methylthio)-1,2,4,5-tetrazine (**3**) was obtained, m.p. 38-39° from light petroleum in 60% of yield [lit. m.p. 37-38.5° (12)].

(6-Hydrazino-1,2,4,5-tetrazin-3-ylthio)acetic Acid (**6**).

To a suspension of 5 g. (0.019 mole) of **2** in methanol (96 ml.) was added dropwise a solution of 2.7 g. (0.054 mole) of hydrazine hydrate in methanol (15 ml.) with stirring at room temperature. The solution was immediately decanted from gums formed during the addition and was stirred for 2 hours again at room temperature, allowing the precipitation of an orange solid, which was collected by filtration, affording **6** as the hydrazine salt (3.2 g., 72%). After rest overnight in refrigerator, a second crop of 0.4 g. (9%) was obtained from the solution, while the work-up of the gums with methanol gave another 0.3 g. (7%). A sample was crystallized for analytical purposes from ethanol, m.p. 118-123°.

(6-Amino-1,2,4,5-tetrazin-3-ylthio)acetic Acid (**7**).

To a suspension of 1.71 g. (0.0065 mole) of **2** in methanol (45 ml.) was added dropwise a solution of ammonia (5.5 mmoles/ml.) in methanol (6 ml.). After stirring overnight at room temperature, a little of **2**, which remained as a solid, was filtered and discarded. The solution was concentrated *in vacuo* to half its volume three times obtaining three crops which were collected together affording 0.73 g. (55%) of **7** as the ammonium salt. By complete evaporation of the solvent, 0.63 g. of **7** were obtained as a crude compound. A sample of the ammonium salt was purified dissolving in water, acidifying to *p*H 2 and extracting with diethyl ether. The solid obtained after evaporation of the solvent was the free acid **7**, m.p. 156-158°; ir: 3460, 3380, 3350, 1710, 1620, 1410, 1195, 950 cm^{-1}.

Monosubstituted 1,2,4,5-Tetrazines (**8**), (**9**), and (**14**).

General Procedure.

A solution of copper sulfate pentahydrate (7.16 g., 0.0287 mole) in water (80 ml.) was added dropwise at room temperature to the hydrazino derivative (0.01 mole) dissolved in 30 ml. of 7.5 buffer solution for **6** and **13** and in 11 ml. of 1*N* sulfuric acid for **4**. A black precipitate formed at once during which time the *p*H was monitored and nitrogen was developed. After stirring for two hours again, the mixture was extracted continously or several times (at least ten) with diethyl ether. After evaporating the solvent to dryness, with many precautions in the case of **8** because of its volatility, crude **8** (35%), **9** (52%) and **14** (40%) were obtained. Compound **8** was crystallized from diethyl ether-light petroleum, after standing for two days at -20° and filtering quickly, m.p. 29-30°; ir: 3090, 2940, 1400, 1220, 1030, 890 cm^{-1}. Compound **9** was purified by column chromatography on silica gel using as eluent chloroform and chloroform-methanol (10:1). The solid resulting from fractions 9-16 was crystallized from diethyl ether, m.p. 124-125°; ir: 1700, 1260, 1200, 1020, 890 cm^{-1}. Compound **14** was purified by column chromatography on silica gel, eluent benzene-ethyl acetate (9:1) and ethyl acetate-acetic acid (9:1), and finally crystallized from diethyl ether-light petroleum, m.p. 89°; ir: 1730, 1350, 1180, 1040, 890 cm^{-1} in chloroform.

3-Bromo-6-(methylthio)-1,2,4,5-tetrazine (**10**).

A solution of 48 g. of ferric sulfate in boiling water (92 ml.) was added dropwise to 7.5 g. (0.0474 mole) of **4** dissolved in 48% hydrobromic acid (90 ml.) with stirring at room temperature. Ten minutes after the end of the addition, the reaction was complete as shown by tlc (benzene 7-ethyl acetate 3). The mixture was extracted with diethyl ether several times (10 x 50 ml.) and the organic layer was washed twice with a 5% solution of sodium sulfite and finally with water. After evaporation of the solvent **10** was obtained as a deep red oil (5.8 g., 59%), which was used in the following step without further purification. A sample was purified by column chromatography on silica gel (eluent diethyl ether 3-light petroleum 7) to afford an oil analytically pure. In the same way, **11** was prepared in 75% of yield, m.p. 31-33°.

6-(Methylthio)-1,2,4,5-tetrazine-3-acetic Acid (**12**).

A mixture of 3.24 g. (0.0312 mole) of malonic acid and 7 ml. (0.0334 mole) of hexamethyldisilazane in benzene (25 ml.) was heated at reflux for 3 hours affording a quantitative yield of the

bis(trimethylsilyl) derivative. After elimination of the ammonia formed *in vacuo*, the solution was added to a suspension of 1.37 g. of 60% sodium hydride (0.0343 mole), which was washed from vaseline by stirring in light petroleum and by successive decantation, in benzene (10 ml.). The addition was regulated in order to maintain the temperature near 40°. After one hour of stirring, during this time the sodium salt precipitated as a gel, a solution of 3.6 g. of crude **10** (90% of purity, 0.0157 mole) in benzene (15 ml.) was added dropwise at 35-40° to the preceding suspension. The dark red mixture was stirred for 2 hours and then added to 5 ml. of 36% hydrochloric acid, under cooling with running water. The organic layer, washed with water, was concentrated to a small volume *in vacuo* and extracted with 5% sodium bicarbonate. The aqueous phase, after layering with diethyl ether, was acidified to *p*H 2 with 15% hydrochloric acid. The solvent was evaporated to dryness under reduced pressure affording 0.9 g. (31%) of **12** as a red solid, which was crystallized from diethyl ether-light petroleum, m.p. 96°; ir: 1730, 1350, 1200, 1080, 890 cm^{-1}.

6-Hydrazino-1,2,4,5-tetrazine-3-acetic Acid (**13**).

Following the procedure above described for the preparation of **6**, 1.4 g. (0.0075 mole) of **12** gave 1.2 g. (79%) of **13**, as the hydrazine salt, m.p. 136-139° from ethanol.

Diethyl 6-Phenyl-1,2,4,5-tetrazine-3-malonate (**16**).

To sodium hydride (60%, 0.260 g., 0.0065 mole) suspended with stirring in anhydrous benzene (10 ml.), after being washed as above described, a solution of 1.14 ml. (0.00747 mole) of diethylmalonate in benzene (40 ml.) was added dropwise at room temperature. The mixture was then heated at reflux for 2 hours. Compound **15** (1.19 g., 0.005 mole) dissolved in the least amount of benzene was then added dropwise to the preceding suspension. A tlc control (light petroleum 7-diethyl ether 3) showed a complete reaction at the end of the addition. After cooling to room temperature, the solid obtained (~ 3 g.) was filtered, suspended in water and extracted twice with chloroform. The red oil obtained after evaporation of the solvent was crystallized from light petroleum affording 1.1 g. (69%) of **16**, m.p. 63-65°; ir: 1750, 1740, 1600, 1400, 1180, 1090, 1040, 850 cm^{-1}.

3-Ethoxy-6-phenyl-1,2,4,5-tetrazine (**17**).

The sodium salt of diethyl malonate was prepared dissolving in 30 ml. of ethanol 0.44 ml. (0.00288 mole) of diethylmalonate and 60 mg. (0.0026 mole) of sodium and refluxing for half an hour. After cooling to room temperature, 0.6 g. (0.0025 mole) of **15** was added to the preceding solution and the red mixture was then heated at reflux for 2 hours. The oily residue, obtained after evaporation *in vacuo* of the solvent, was dissolved in chloroform and chromatographed on a column of silica gel (50 g.), using as eluent light petroleum-ether (7:3), affording 0.106 g. (21%) of **17**, m.p. 103-105° after crystallization from light petroleum.

Compound **17** was also obtained in 75% of yield by mixing in benzene equimolar quantities of **15** and sodium ethoxide.

(6-Phenyl-1,2,4,5-tetrazin-3-ylthio)acetic Acid (**18**).

To a stirred solution under nitrogen of 0.505 g. (0.0055 mole) of mercaptoacetic acid and 1.11 g. (0.011 mole) of *N*-methylmorpholine in chloroform (30 ml.) a solution of 1.2 g. (0.005 mole) of **15** in chloroform (20 ml.) was added at room temperature. After stirring half an hour, 10 ml. of 15% hydrochloric acid was added to the solution; the organic layer, washed with water, was concentrated to the volume of 10 ml. The solid obtained was filtered giving 0.85 g. (68%) of **18**, m.p. 160-162°; ir: 1710, 1420, 1350, 1190, 1075, 1040, 910 cm^{-1}.

6-Phenyl-1,2,4,5-tetrazine-3-acetic Acid (**19**).

Following the method for the synthesis of **12**, the acid **19** was prepared in 83% of yield, by concentrating the benzene layer, filtering the red solid which was freed from the excess of malonic acid by suspension in water, m.p. 139-140° after crystallization from benzene; ir: 1730, 1600, 1420, 1390, 1200, 1095, 1020, 900 cm^{-1}.

The methyl ester was prepared by reaction with 3-methyl-*p*-tolyltriazene (Aldrich) (30), m.p. 85-88° from chloroform-light petroleum; ir: 1740 cm^{-1}; nmr: δ 3.75 (s, 2), 4.41 (s, 3), 7.5-7.7 (m, 5) in deuteriochloroform.

3-Methyl-6-phenyl-1,2,4,5-tetrazine (**21**) was obtained heating **19** at 130°/20 mm. Crystallization from light petroleum afforded an analytical sample, m.p. 70-72°; ir: 1400, 1370, 1090, 890 cm^{-1}; nmr: δ 3.08 (s, 3), 7.5-7.7 (m, 5) in deuteriochloroform.

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