

salts with cyanamide, amines with alkylisouronium or alkylisothiuronium salts, or amines with 3,5-dimethyl-1-guanylpurazole<sup>3</sup>. The last two methods, generally better than the cyanamide method<sup>3</sup>, have usually required a strongly basic medium and/or heat when applied to the guanylation of amino acids<sup>4,5</sup>. Isolated yields for this guanylation by the purazole method were not reported<sup>4</sup>. Lately, some efficient guanidine syntheses using substituted aminoiminomethanesulfinic acids or aminoiminomethanesulfonic acids or isothiurea S-oxides have been reported in patents<sup>6-8</sup>. Since there had not been a systematic study of the effect of structure on reactivity in either the S-oxide or the amine, we decided to study the reactions of aminoiminomethanesulfinic acids and aminoiminomethanesulfonic acids (**2**) with amino acids. The only description of these reactions was by Walter, who used aminoiminomethanesulfinic acid as the guanylation agent. He reported that its reaction with glycine in the presence of ammonia gave a 34% yield of *N*-(aminoiminomethyl)glycine. The same paper claimed that alanine, 4-aminobutanoic acid and norleucine also reacted to give the corresponding guanidino compounds, but no yields were reported<sup>9</sup>.

Only the aminoiminomethanesulfonic acids (**2**) were studied in detail, because early in this work it was found that aminoiminomethanesulfinic acid gave much poorer yields than aminoiminomethanesulfonic acid (**2a**). Our results with **2a**, *N*-phenylaminoiminomethanesulfonic acid (**2b**), and *N,N'*-diphenylaminoiminomethanesulfonic acid (**2c**) with various amino acids, are given in Tables 1, 2 and 3, respectively<sup>10</sup>. These reactions required only one equivalent of potassium carbonate, and occurred at ambient temperature in a few minutes for **2a** and in a few days for **2c**. With few exceptions isolation and purification of the products were very simple: the products precipitated from the reaction mixture and could be purified by recrystallization. In some cases, e.g. **2a** with DL-alanine, L-isoleucine or L-leucine, the products were soluble in the reaction medium and were difficult to isolate as pure solids. Apparently a similar problem was encountered by Pant<sup>5</sup>. Also, attempted alternate syntheses of the products of Table 2 using *S*-methyl-*N*-phenylisothiuronium iodide, the amino acid, and base gave mixtures from which product could not be readily isolated. Similarly, no guanidino product could be isolated from

reactions of glycine with *S*-methyl-*N,N'*-diphenylisothiuronium iodide, even under forcing conditions. Thus the synthesis of the di- and tri-substituted guanidines by our

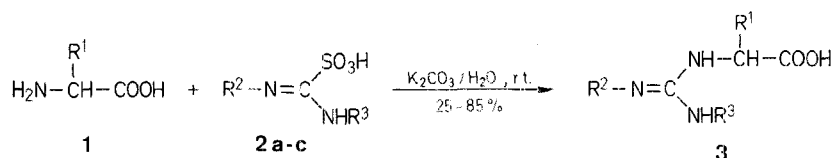
### A Facile Conversion of Amino Acids to Guanidino Acids<sup>1,2</sup>

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The conversion of amino acids to guanidino acids by the action of aminoiminomethanesulfonic acids (**2a-c**) is reported. Compounds **2a-c** were synthesized by peracetic acid oxidation of the corresponding thioureas.

Until quite recently the common methods for producing guanidino compounds from amines have been to treat amine



2	R <sup>2</sup>	R <sup>3</sup>
a	H	H
b	C <sub>6</sub> H <sub>5</sub>	H
c	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>

**Table 1.** Guanidino Acids<sup>a</sup> from Reactions of **2a** with Amino Acids

Amino Acid	Yield [%]	Exp. m.p. <sup>b</sup> [°C]	Lit. m.p. [°C]
3-aminopropanoic acid	75	217–218	216 <sup>12</sup>
DL-alanine	5	240.5–241.5 <sup>c</sup>	188 <sup>12</sup> 204 <sup>13</sup>
p-aminobenzoic acid	80	310–3	310 <sup>14</sup> 260–270 d <sup>15</sup>
4-aminobutanoic acid	50	281–282 <sup>d</sup>	248 <sup>16</sup>
5-aminopentanoic acid	55	289–291 <sup>e,f</sup>	267–271 <sup>17</sup>
glycine	80	chars <sup>f</sup>	270–280 <sup>18</sup>
L-isoleucine	5	240–240.5	245 <sup>16</sup>
L-leucine	g		
DL-methionine	60	195.5–196	173 <sup>12</sup> 193–194 <sup>19</sup>
L-phenylalanine	45	261.5–264 <sup>e,f</sup>	> 200 d <sup>20</sup> 204 d <sup>12</sup>
L-proline	g		
DL-serine	50	246–246.5 <sup>c</sup>	200 d <sup>20</sup> 205 d <sup>12</sup>
DL-valine	55	255–256.5 <sup>e,f</sup>	272 <sup>16</sup>

<sup>a</sup> All products had 3 distinctive IR bands in the regions 1640–1680, 1540–1590, 1380–1410 cm<sup>-1</sup>.

<sup>b</sup> All compounds decomposed at their m.p.

<sup>c</sup> Satisfactory microanalyses obtained: C, H, N ± 0.30.

<sup>d</sup> M.P. of authentic sample (Calbiochem.), 283–285° d; mixture melting point 282–283° d.

<sup>e</sup> Mixture melting point with an authentic sample, prepared by the method of Ref. 13, showed no depression.

<sup>f</sup> The infrared spectrum was identical to that of an authentic sample.

<sup>g</sup> TLC showed that some guanidino compound was produced, but a pure sample could not be isolated.

**Table 2.** Guanidino Acids<sup>a</sup> from Reactions of **2b** with Amino Acids

Amino Acid	Yield [%]	Exp. m.p. <sup>b</sup> [°C]	Lit. m.p. [°C]
3-aminopropanoic acid	70	277–278.5 <sup>c</sup>	234 <sup>21</sup>
p-aminobenzoic acid	65	239–249 <sup>d</sup>	
4-aminobutanoic acid	e		
glycine	85	256–256.5	256 d <sup>22</sup>
L-leucine	f		

<sup>a</sup> All products had 3 distinctive IR bands in the regions 1640–1660, 1540–1580, 1360–1400 cm<sup>-1</sup>.

<sup>b</sup> All compounds decomposed at their m.p.

<sup>c</sup> Satisfactory microanalysis obtained: C, H, N ± 0.30.

<sup>d</sup> Solubility properties of this compound and its salts as well as its instability on heating, precluded preparation of an analytical sample.

<sup>e</sup> Phenylurea was isolated in 12% yield.

<sup>f</sup> Phenylurea was isolated in 65% yield.

method is clearly superior to their synthesis from isothiourea compounds. The lower yields of products from **2c** can be attributed to electronic and steric effects on the several possible reaction pathways. These are being studied in more detail in another connection.

**2b** is a known compound<sup>23</sup>. Although **2a** has been reported in the literature<sup>24</sup>, details of its synthesis have not. Because reproducible formation of pure, stable **2a** requires care, a specific procedure for its synthesis is given. **2c**, a new compound, was synthesized in a similar manner.

**Table 3.** Guanidino Acids<sup>a</sup> from Reactions of **2c** with Amino Acids

Amino Acid	Yield [%]	Exp. m.p. <sup>b</sup> [°C]	Molecular Formula
3-aminopropanoic acid	25	216–220	C <sub>16</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> <sup>c</sup> (283.3)
p-aminobenzoic acid	25	260	C <sub>16</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> <sup>d</sup> (319.4)
glycine	35	211–216	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub> <sup>c</sup> (267.3)

<sup>a</sup> All products had 3 distinctive IR bands in the regions 1650–1670, 1520–1590, 1360–1400 cm<sup>-1</sup>.

<sup>b</sup> All compounds decomposed at their m.p.

<sup>c</sup> Satisfactory microanalyses obtained: C, H, N ± 0.30.

<sup>d</sup> Microanalysis:

calc.	C 72.49	H 5.17	N 12.68
found	72.06	5.11	12.73

#### Aminoiminomethanesulfonic Acid (**2a**):

Peracetic acid is prepared by slowly adding acetic anhydride (50 ml) to 30% hydrogen peroxide (45 g) cooled in an ice bath. The addition of two drops of concentrated sulfuric acid causes a violent reaction. After the reaction has subsided, acetic anhydride (110 ml) is slowly added to the cooled mixture. The mixture is allowed to warm gradually to room temperature and left to stand for at least one day. Then methanol (160 ml) is added and the solution is cooled to 10°C in an ice bath. A solution of thiourea (10 g) in methanol (500 ml) is also cooled. The latter is added to the oxidizing mixture in portions at such a rate as to maintain the temperature at 10–20°C. (Cooler reaction mixtures led to more aminoiminomethanesulfonic acid as product.) If a solid forms while thiourea is being added, the solution is allowed to warm to a higher temperature. After the addition is complete, the mixture is allowed to stand at room temperature for one day. Any crystals that formed (mostly aminoiminomethanesulfonic acid) are removed by filtration and discarded. After the filtrate is concentrated to about 100 ml, the solid is filtered and washed with several portions of cold methanol; yield: 51–83%; m.p. ~ 125°C (with bubbling and formation of a new solid (Lit.<sup>25</sup> m.p. 112–115°C).

IR (KBr)  $\nu = 1220$  (s), 1050 (s) cm<sup>-1</sup>. (These peaks are not present in the infrared spectrum of aminoiminomethanesulfonic acid).

The product can be recrystallized from a large volume of glacial acetic acid. Drying **2a** *in vacuo* (1–2 mm) over KOH at room temperature improves stability and m.p., 131–131.5°C. If stored in the refrigerator, it is stable for at least 5 months.

#### N-Phenylaminoiminomethanesulfonic Acid (**2b**):

The synthesis of **2b** is similar to that for **2a** with the following differences: (a) the peracetic acid is not diluted with methanol (b) the reaction temperature is maintained at 0–10°C, and (c) no

solid is present after the oxidation step. **2b** is obtained as a white solid in 53% yield, m. p. 161–161.5°C d (Lit.<sup>2,3</sup> m. p. 171–172°C d). IR (KBr):  $\nu = 1666$  (s), 1253 (s, broad), 1060 (s), 639 (s)  $\text{cm}^{-1}$  (Lit.<sup>2,3</sup> 1245, 1234, 1065  $\text{cm}^{-1}$ )

#### *N,N'*-Diphenylaminoiminomethanesulfonic Acid (**2c**):

**2c** is prepared by a procedure analogous to that for **2a** and **2b**. Cooled, freshly prepared peracetic acid (three equiv), undiluted by solvent, is slowly treated with a cooled solution of diphenylthiourea (5.008 g, 22 mmol) in methylene chloride (350 ml), at such a rate to maintain the temperature of the reaction at 2–5°C. Upon complete addition of the diphenylthiourea solution, white needles are present. As the mixture warms to room temperature, more solid forms. The reaction is allowed to stand one day at room temperature and the white solid is collected. This is a mixture of the desired product and bisanilinium sulfate salt (IR identical to authentic sample) and is discarded. The filtrate is concentrated to 50 ml, the white solid filtered and washed with methylene chloride to give **2c**; yield: 5.0 g (83%); m. p. 213.5–214°C.

Repeated recrystallizations from methanol/ether give white crystals: m. p. 209–209.5°C d.

$\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_3\text{S}$  calc. C 56.51 H 4.38 N 10.14 S 11.60  
(276.3) found 56.51 4.49 9.93 11.51

IR ((KBr):  $\nu = 3468$  (m, broad), 3168 (m–s, broad), 1630 (s), 1260 (s), 1233 (s), 1052 (s), 638 (s)  $\text{cm}^{-1}$ ).

#### Guanylation Reactions; General Procedure:

In a 50 ml Erlenmeyer flask are mixed potassium carbonate, (1.38 g, 0.01 mol) water (10 ml), and the appropriate amino acid (0.01 mol). If the amino acid is not completely soluble, a small portion of water is added and the mixture heated. This process is repeated until all of the amino acid dissolves. Then solid **2a**, **b** or **c** (0.01 mol) is added in small spatulafuls over a period of approximately 10 minutes, with good swirling after each addition. During some additions there is bubbling and formation of a precipitate (see below). The reaction mixture is allowed to sit uncovered at room temperature 24 h and then filtered. The white solid is allowed to air dry and is then characterized by melting point, IR and, where necessary, by elemental analysis. The filtrate is allowed to sit uncovered at room temperature over a period of days and further crops of product are collected and characterized.

In the reactions of 3-aminopropanoic acid, DL-alanine, and L-isoleucine with **2a**, the products do not readily precipitate. In these cases the solvent is removed from the reaction mixture by rotary evaporation. The residue is stirred with water (1–4 ml) and any insoluble material is collected by suction filtration, washed with acetone and dried. If the solid contains potassium sulfate it is further purified by recrystallization from boiling water.

In the reactions with **2c**, any precipitate formed during the 0.5 h after complete addition is removed by suction filtration. This solid, the potassium salt of **2c**, is washed with water; yield (~30%); no melting to 400°C.

IR (KBr):  $\nu = 3443$  (s), 1232 (s), 1216 (s), 1189 (s), 1037 (s)  $\text{cm}^{-1}$ .

Because of its instability to heating in water and its insolubility in organic solvents, an analytical sample is prepared by mixing dust-free solutions of **2c** and potassium carbonate and collecting and drying the precipitate formed.

$\text{C}_{13}\text{H}_{11}\text{N}_2\text{SO}_3\text{K}$  calc. C 49.66 H 3.53 N 8.91 S 10.20  
(314.4) found 50.09 3.47 8.99 9.84

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<sup>2</sup> Independent work on the reactions of aminoiminomethanesulfonic and sulfonic acids was developed by R. C. Stanzione, J. N. Plampin, J. E. Mills and C. A. Maryanoff. Their work was reported at the 190th American Chemical Society Meeting (ORGN 112).

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<sup>1</sup> This work was presented at the 190th American Chemical Society Meeting in Chicago, Illinois, 1985, ORGN 203.