Synthesis of Cyclic Guanidines[1]

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A method is described whereby a variety of cyclic guanidines may be prepared *via* the intermediacy of tosyl-protected cyclic guanidines; the latter compounds are easily available from the reactions of both aliphatic and aromatic diamines with *S,S*-dimethyl-*N*-tosyliminodithiocarbonimidate. The detosylation reaction which results in guanidine formation proceeds quantitatively in anhydrous hydrogen fluoride.

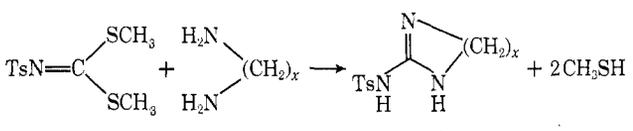
The observation that *S,S*-dimethyl-*N*-tosyliminodithiocarbonimidate (**1**) reacts with ethylenediamine and *o*-phenylenediamine to give high yields of the *N*-tosyl cyclic guanidines **2a** and **3**[3] prompted us to examine the possible general usefulness of this reagent for the generation of cyclic guanidines. This approach appeared to be especially attractive in view of a recent report from the peptide field which described the removal of the tosyl group from the guanido group of arginine using anhydrous hydrogen fluoride.[4] We now report that **1** reacts with a variety of aliphatic and aromatic diamines to give easily isolable tosyl-protected cyclic guanidines and that the usually difficult detosylation process[5] can be carried out in anhydrous hydrogen fluoride to give cyclic guanidines; the detosylation step is quantitative.

There are methods available for the synthesis of cyclic guanidines from diamines, both aliphatic and aromatic. Thus 2-amino-2-imidazoline and 2-aminobenzimidazole can be obtained as their salts by the action of cyanogen bromide on ethylenediamine and *o*-phenylenediamine, respectively,[9-11] and 2-amino-2-imidazoline is also available by the action of cyanamide or dimethylcyanamide on ethylenediamine monotoluene-*p*-sulfonate.[12] The latter method has also been extended to the preparation of the six-membered cyclic guanidine, 2-amino-3,4,5,6-tetrahydropyrimidine.[12] A second approach to cyclic guanidines in wide use involves the reaction of amines with 2-methylthio-1,3-diazines (available in two steps from diamines); this procedure has been used to prepare *N*-alkylguanidines of a wide variety.[13-15] Two other routes into the cyclic guanidine system, which have limited applicability, are hydrogenation of a 2-aminopyrimidine to obtain a 2-amino-3,4,5,6-tetrahydropyrimidine[16] and the fusion of guanidine with 4,5-diamino-6-hydroxypyrimidine to afford 8-amino-6-hydroxypurine.[17] We now report a synthesis *via* *S,S*-dimethyl-*N*-tosyliminodithiocarbonimidate as an alternative to the above. Inherent in this approach is the attractiveness of the intermediacy of the tosyl-protected guanidine which conceivably could be subjected to further chemical operations before the detosylation step required to generate a free guanidine.[18]

Synthesis of Tosyl-Protected Cyclic Guanidines.—*S,S*-Dimethyl-*N*-tosyliminodithiocarbonimidate (**1**) is a stable compound which can be easily prepared in high yield.[1] The reaction of **1** with aliphatic diamines proceeds readily in refluxing aqueous ethanol to give cyclic tosylguanidines in high yields. In addition to the guanidine a second product is produced which is insoluble in the hot reaction medium and which can be removed from the tosylguanidine by filtration; mass spectral data indicate these second products are compounds of high molecular weight and thus are probably polymeric in nature. In Table I are given the details of the reaction of **1** with four aliphatic diamines. The diamines were used directly or were generated *in situ* from their dihydrochlorides; the "polymeric" side products were removed by filtration of the hot reaction solution.

TABLE I

REACTION OF *S,S*-DIMETHYL-*N*-TOSYLIMINODITHIOCARBONIMIDATE (**1**) WITH ALIPHATIC DIAMINES



1 **2**

Diamine, X	Time, hr	Yield, % "Polymer"	Yield, % Tosylguanidine, **2**
2	4	0	**a**, 87
3	9	6	**b**, 79
4	24	16	**c**, 76
6	48	100	**d**, 0

An unsymmetrical (*i.e.*, substituted) aliphatic diamine was next chosen for investigation. With the aim of preparing an optically active intermediate which might be potentially useful for the synthesis of the novel guanido amino acid capreomycidine (**5**),[16] we prepared the op-

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(1) Supported in part by the U. S. Army Research Office, Durham, N. C.

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(3) R. Gompper and W. Hagele, *Chem. Ber.*, **99**, 2885 (1966).

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(5) The methods usually used to effect detosylation were not attempted; however, in view of the fact that these methods (*e.g.*, sodium in liquid ammonia,[6] HBr in phenol,[7] PH_4I in the presene of HI[8]) are less than satisfactory from point of view of yield, mildness of reaction conditions, and ease of operation, the HF procedure was clearly superior.

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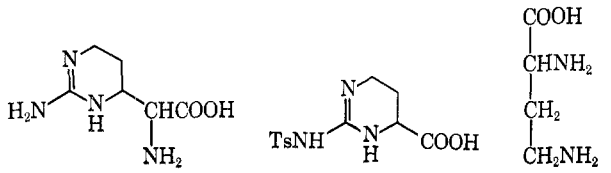
(18) The presence of the tosyl group on the guanidine moiety considerably reduces the basicity of this ordinarily strongly alkaline group. We have found that tosyl-protected guanidines do not form salts in the presence of HCl, whereas guanidines and acylguanidines do.

tically active tosylguanidine **6**. The required optically active 2,4-diaminobutyric acid (**7**) was available from



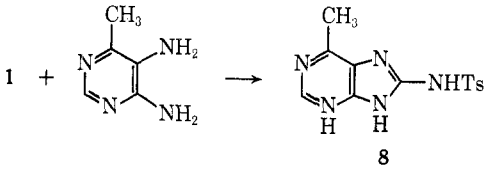
5 **6** **7**

L-(+)-glutamine acid *via* a Schmidt rearrangement.[19] The unsymmetrical tosyl-protected cyclic guanidine was obtained in 83% yield by the reaction of the sodium salt of (+)-2,4-diaminobutyric acid (**7**) with **1** in refluxing aqueous ethanol followed by acidification of the reaction medium to regenerate the acid. Due to the low solubility of the tosyltetrahydropyrimidine **6**, optical rotation was not measured; however, the detosylated guanidine (see below) proved to be optically active.

No attempts were made to prepare *N*-alkylguanidines by this method since other work with **1** has shown that it is unreactive toward secondary amines. However, **1** can easily be converted to the dichloro compound;[20] the latter has been demonstrated to be highly reactive to secondary amines[21] and thus could conceivably be a useful reagent for the generation of *N*-alkyl cyclic guanidines corresponding to *N*-alkyl derivatives of **2**.

The general usefulness of the *N*-tosyldichlorocarbonimidate for the preparation of cyclic guanidines is, however, limited by the fact that an extra equivalent of the diamine (or some other base) is required in the reaction medium to neutralize the released acid. Dithio compound **1** requires, of course, only 1 equiv of diamine since the weak and volatile conjugate acid of CH_3S^- is released during the reaction.

The reactivity of **1** toward aromatic diamines is reduced considerably from that observed for its reaction with aliphatic diamines. Thus the tosylguanidine 2-*p*-tosylaminobenzimidazole (**3**) can be obtained in 72% yield from the reaction of **1** with *o*-phenylenediamine in DMF at 150–160° for 12–16 hr.[1] This procedure is quite similar to that[22] in which 2-benzenesulfonylaminobenzimidazole could be obtained by fusing *o*-phenylenediamine with benzenesulfonylguanidine. We have extended the reaction of **1** with aromatic diamines to the case of 6-methyl-4,5-diaminopyrimidine and have found that, at 150° in DMF for 16 hr, a 58% yield of 6-methyl-8-tosylaminopurine (**8**) is obtained.



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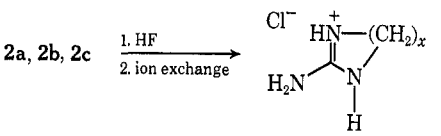
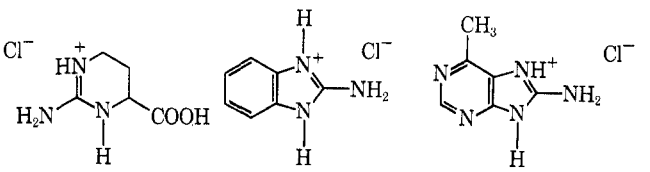
Detosylations Using Anhydrous Hydrogen Fluoride.—Detosylations of the six tosylguanidines described above were effected in anhydrous HF in a system similar to that diagrammed by Lenard.[23] Liquid HF was dried over cobalt fluoride, distilled into the reaction vessel, and subsequently removed without exposure to air or moisture. The residue was partitioned between benzene and water and the benzene extract contained the removed tosyl portion of the reaction mixture, which was characterized as tosyl fluoride.

The cyclic guanidines, as HF salts in water, were applied to an ion-exchange column, the HF was eluted with water, and the guanidine (as its hydrochloride) was removed with 4 *N* HCl. Evaporation left the guanidine salts which could be crystallized from isopropyl alcohol–ether. The products were quite hygroscopic and in all cases the yields were essentially quantitative (97–100%). The carboxy-substituted cyclic guanidine (**10**) proved to be optically active ($[\alpha]^{25}D$ +144°) and thus of potential value as an asymmetric intermediate in the synthesis of capreomycidine (**5**).

There seems to be no doubt as to the usefulness of anhydrous HF as a detosylating reagent for tosyl-protected guanidines. However, it is known that *p*-toluenesulfonamides are inert to this reagent. Sakakibara, *et al.*,[24] have reported that the tosyl group



9a, $x = 2$
9b, $x = 3$
9c, $x = 4$



10 **11** **12**

is not removed from tosyl-protected peptides under conditions in which a large number of protective groups can be removed from peptides (20° for periods of 30 min to 2 hr). We have found that *p*-toluenesulfonamide and tosylglycine are recovered completely intact after 24 hr exposure to anhydrous HF. Thus the applicability of the HF detosylation procedure is limited, but the bounds of its limitations have yet to be defined.

Experimental Section[25]

2-*p*-Toluenesulfonylamino-2-imidazoline (2a).—Ethylenediamine dihydrochloride (951 mg, 7.15 mmol) was dissolved in 5 ml of water and 14.3 ml of 1 *N* NaOH was added. Ethanol (75 ml) was added along with *S*,*S*-dimethyl-*N*-tosyliminodithiocarbonimidate[1] (**1**) (1.94 g, 7.15 mmol). The mixture was refluxed for 4 hr and then filtered, and the filtrate was taken to one-third of the original volume. Water was added to cloudiness, the solution was cooled, and the product crystallized as colorless

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(25) Nmr spectra were determined with a Varian T-60 instrument using tetramethylsilane as an external standard (δ 0). Melting points, uncorrected, were determined on a Büchi melting point apparatus. Uv spectra were recorded in H_2O using a Cary Model 14 spectrophotometer. Mass spectra were obtained with Varian M-66 and CEC-21-110B instruments. Optical rotations were measured on a Bendix ETL-NPL automatic polarimeter. Microanalyses were performed by the Analytical Laboratories, University of California at Berkeley.

needles, mp 224–227.5°. Recrystallization from acetone gave material of mp 227–227.5° (lit.[3] mp 230–32°) in 1.47 g, 87% yield, mass spectrum *m/e* 239 (M^+), *m/e* 175 ($M^+ - 64$).[26]

2-*p*-Toluenesulfonylamino-3,4,5,6-tetrahydropyrimidine (2b).—The procedure was the same as that used for **2a** except that the diamine used was freshly distilled 1,3-diaminopropane, the reaction solvent was 95% ethanol, and the reaction time was 9 hr. The product was obtained as colorless needles from acetone: mp 264–267 (79% yield); mass spectrum *m/e* 253 (M^+) *m/e* 189 ($M^+ - 64$).

Anal. Calcd for $C_{11}H_{15}N_3O_2S$: C, 52.2; H, 6.0; N, 16.6; S, 12.7. Found: C, 52.2; H, 5.9; N, 16.7; S, 12.6.

2-*p*-Toluenesulfonylamino-4,5,6,7-tetrahydro-1,3-diazepine (2c).—The procedure, using 1,4-diaminobutane dihydrochloride, was identical with that used for **2a** except that the reaction time was 24 hr. The colorless crystals from acetone (76% yield) had mp 221–233°, mass spectrum *m/e* 267 (M^+), 203 ($M^+ - 64$).

Anal. Calcd for $C_{12}H_{17}N_3O_2S$: C, 53.9; H, 6.4; N, 15.7; S, 12.0. Found: C, 54.0; H, 6.3; N, 15.8; S, 11.8.

2,4-Diaminobutyric Acid Dihydrochloride (7).—The procedure used was that of Adamson,[18] with an improvement in the work-up. Sodium azide (4 g, 0.062 mol) was added in small portions to L-(+)-glutamic acid (7.35 g, 0.050 mol), 25 ml of concentrated sulfuric acid, and 15 ml of chloroform and the mixture was stirred at 45°. After 3 hr, the reaction mixture was poured onto 200 ml of ice and the resulting aqueous solution was treated with hot saturated barium hydroxide solution until no longer acid to congo red. Barium sulfate was removed by centrifugation and the aqueous solution was reduced to 100 ml by reduced pressure distillation and then applied to a 100-ml Bio-Rad AG 50W-X (50–100 mesh) ion-exchange column. The column was eluted with 300 ml of 0.1 *N* HCl which removed all of the unreacted glutamic acid as its hydrochloride (4.30 g, 58% recovery). The product was eluted with 1 l. of 1 *N* HCl, the water was removed at reduced pressure, and the residue was ground with absolute ethanol, collected by filtration and dried, mp 199–201° dec. The yield was 3.70 g (91% based on consumed glutamic acid): $[\alpha]^{25}D$ +15.0° (*c* 3.50, water) [lit.[18] mp 195–196, $[\alpha]^{18}D$ +14.6° (*c* 3.67, water)] [lit.[28] mp 204°, $[\alpha]^{25}D$ +15.1° (*c* 3.82, water)].

2-*p*-Toluenesulfonylamino-4-carboxy-3,4,5,6-tetrahydropyrimidine (6).—(+)-2,4-Diaminobutyric acid dihydrochloride (7) (1.09 g, 5.70 mmol) was dissolved in 17.1 ml of 1 *N* NaOH. Ethanol (75 ml) and *S,S*-dimethyl-*N*-tosyliminodithiocarbonimidate (1) (1.57 g, 5.70 mmol) were added and the reaction mixture was refluxed for 12 hr and cooled, and 5.7 ml of 1 *N* HCl was added to the solution. The solution was evaporated under reduced pressure to the cloud point and allowed to stand overnight in the cold. The product was collected as colorless plates, mp 202–204° (1.42 g, 83% yield).

Anal. Calcd for $C_{12}H_{15}N_3O_4S$: C, 48.5; H, 5.1; N, 14.1; S, 10.8. Found: C, 48.7; H, 5.3; N, 13.9; S, 10.7.

6-Methyl-8-*p*-toluenesulfonylaminopurine (8).—The procedure was similar to that used for 2-*p*-toluenesulfonylaminobenzimidazole.[1] 4,5-Diamino-6-methylpyrimidine[27] (25.8 mg, 0.208 mmol) was heated at 150° in 6 ml of DMF under a nitrogen atmosphere with *S,S*-dimethyl-*N*-tosyliminodithiocarbonimidate (1) (57.2 mg, 0.208 mmol) for 16 hr. The reaction mixture was cooled to 5° and stored overnight forming pale yellow crystals which were collected and washed with water and dried. The compound was characterized after detosylation (see below).

2-Amino-1,3-imidazolidine Hydrochloride and Isolation of *p*-Toluenesulfonyl Fluoride.—2-*p*-Toluenesulfonylamino-1,3-imidazolidine (**2a**) (716 mg, 3.00 mmol) was stirred at room temperature for 2 hr in *ca.* 3 ml of anhydrous HF in a sealed Kel-F vessel.[23,24] The HF was evaporated and the reaction mixture dried over KOH pellets under high vacuum. The residue was washed into a separatory funnel with three 5-ml portions each of water and benzene, alternatively, the layers were separated, and the water was washed with two 10-ml portions of benzene.

The total benzene extract was dried over Na_2SO_4, evaporated under reduced pressure, and dried in a desiccator overnight giving a residue of *p*-toluenesulfonyl fluoride which crystallized as colorless plates (518 mg, 100%), mass spectrum *m/e* 174 (M^+).

Anal. Calcd for $C_7H_7FO_2S$: C, 48.3; H, 4.1; S, 18.4. Found: C, 48.1; H, 4.2; S, 18.3.

The aqueous layer was reduced to 5 ml and added to a 100-ml Bio-Rad AG 50W-X (50–100 mesh) ion-exchange column. Elution with water until the eluate was neutral (after an initial period when the eluate was acid) was followed by washing with 300 ml of 4 *N* HCl, and the latter eluate was taken to dryness and the residue dried at reduced pressure overnight. The residue was crystallized from isopropyl alcohol–ether as colorless needles of **9a**, mp 118–121°, yield 330 mg (98%).

Anal. Calcd for $C_3H_8N_3Cl \cdot {}^1/_2H_2O$: C, 27.7; H, 6.8; N, 32.0. Found (hygroscopic): C, 28.2; H, 6.5; N, 31.6.

2-Amino-3,4,5,6-tetrahydropyrimidine Hydrochloride (9b).—2-*p*-Toluenesulfonylamino-3,4,5,6-tetrahydropyrimidine (**2b**, 330 mg, 1.30 mmol) was treated with anhydrous HF as described above. The residue, after ion-exchange chromatography, was recrystallized from isopropyl alcohol–ether and gave colorless needles of **9b** (177 mg, 101%), mp 127–129.5°.

Anal. Calcd for $C_4H_{10}N_3Cl$: C, 35.4; H, 7.4; N, 31.0. Found (hygroscopic): 35.2; H, 7.4; N, 30.8.

2-Amino-4,5,6,7-tetrahydro-1,3-diazepine Hydrochloride (9c).—2-*p*-Toluenesulfonylamino-4,5,6,7-tetrahydro-1,3-diazepine (**2c**) (267 mg, 1.0 mmol) was treated with anhydrous HF as described above. The residue, after ion-exchange chromatography, was recrystallized from isopropyl alcohol–ether and gave colorless needles of **9c** (149 mg, 98%), mp 129–132°.

Anal. Calcd for $C_5H_{12}N_3Cl$: C, 40.1; H, 8.1; N, 28.1. Found: C, 39.9; H, 8.2; N, 27.9.

2-Amino-4-carboxy-3,4,5,6-tetrahydropyrimidine Hydrochloride (10).—4-Carboxy-2-*p*-toluenesulfonylamino-3,4,5,6-tetrahydropyrimidine (**6**) (672 mg, 22.4 mmol) was treated with anhydrous HF as described above. The residue, after ion-exchange chromatography, was recrystallized from isopropyl alcohol–ether and gave colorless needles of **10**: mp 210–211° dec; 383 mg, 95% yield; $[\alpha]^{25}D$ +144° (*c* 1.08, water); nmr δ 4.31 (t, 1 H), 3.32 (m, 2 H), 2.24 (t, 2 H).

Anal. Calcd for $C_5H_{10}N_3O_2Cl$: C, 33.4; H, 5.8; N, 23.4. Found (hygroscopic): C, 33.7; H, 6.1; N, 23.4.

2-Aminobenzimidazole Hydrochloride (11).—2-*p*-Toluenesulfonylaminobenzimidazole (**6**) (322 mg, 1.34 mmol, prepared as described by Gompper and Hagele[3]) was treated with anhydrous HF as described above. The residue, after ion-exchange chromatography, was recrystallized from isopropyl alcohol–ether and gave colorless crystals of **11** (177 mg, 91% yield): mp 209–210°; high resolution mass spectrum *m/e* 133.0643 (M^+ – HCl) (calcd $C_7H_7N_3$: 133.0639).

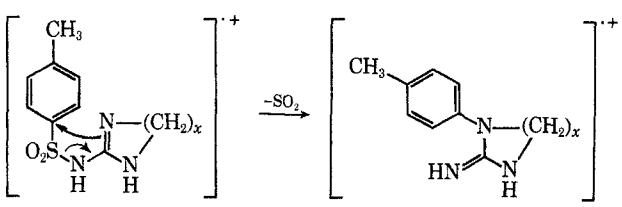
Anal. Calcd for $C_7H_8N_3Cl \cdot {}^1/_2H_2O$: C, 47.2; H, 5.1; N, 23.4. Found (hygroscopic): C, 47.2; H, 5.2; N, 23.2.

8-Amino-6-methylpurine Hydrochloride (12).—6-Methyl-8-*p*-toluenesulfonylaminopurine (**8**, total crude from above) was treated with anhydrous HF as described above. The residue, after ion-exchange chromatography, was recrystallized from isopropyl alcohol–ether to give pale yellow plates: mp 314–317° dec; 21.0 mg, 58% yield based on starting diamine; mass spectrum *m/e* 149 (M^+ – HCl); uv $\lambda_{max}^{H_2O,\ pH\ 2.4}$ 285 nm (ε 17,000); $\lambda_{max}^{H_2O,\ pH\ 7.0}$ 239 nm (ε 3800), 280 (15,100) [lit.[29] for 8-aminopurine; $\lambda_{max}^{H_2O,\ pH\ 2.4}$ 288 nm (ε 15,800); $\lambda_{max}^{H_2O,\ pH\ 7}$ 241 nm (ε 3200), 283 (14,400)].

Anal. Calcd for $C_6H_8N_5Cl \cdot H_2O$: C, 35.4; H, 4.9. Found (hygroscopic): C, 35.9; H, 4.6.

Registry No.—**2a**, 13111-53-0; **2b**, 26893-35-6; **2c**, 26893-36-7; **6**, 26893-37-8; **7**, 26889-08-7; **9a**, 26893-38-9; **9b**, 26893-39-0; **9c**, 26893-40-3; **10**, 26889-09-8; **11**, 26893-41-4; **12**, 26893-42-5; *p*-toluenesulfonyl fluoride, 455-16-3.

(26) The ($M^+ - 64$) peak appears in the mass spectra of all of the nonaromatic cyclic guanidines. It probably arises as follows.



This rearrangement is analogous to that found for sulfonylureas.[27]

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