Routes to Functionalized Guanidines. The Synthesis of Guanidino Diesters[1a]

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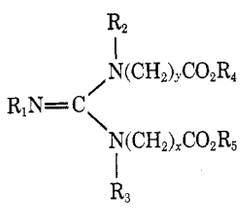
Six general methods for the synthesis of acyclic and cyclic guanidines, of structures 1 and 2 and bearing a variety of substituents, are described. These guanidines may be symmetrical or unsymmetrical, and the substituents they bear provide the basis for further chemical manipulation. The acyclic guanidines are derived from single carbon intermediates, such as **3**, **9**, **13**, and **14**, and the appropriately substituted amine. The cyclic guanidines result from the functionalization of a 2-*p*-toluenesulfonamidopyrimidine which is subsequently hydrogenated. Use of the tosyl as a protecting group reduces the effects of the strongly alkaline guanidine moiety, and its facile removal is achieved with hydrogen fluoride. Detosylation of the tosyl-protected guanidino diester **12** resulted in formation of the imidazolin-4-one **51**; this reaction proved to be general for the guanidines **1**, $x = 1$, and **2**, $z = 1, 2$. These imidazolinones underwent deuterium exchange for which a mechanism involving the formation of a mesoionic intermediate is proposed.

Increasingly among the functional groups found in natural products, there are instances of the occurrence of the guanidine moiety. In addition to the well-known and obvious examples of arginine, creatinine, and creatine (the latter two are classed as glycocyamidines[2]), the guanidino group recently has been found in the puffer fish poison, tetrodotoxin,[3] in the paralytic shellfish poison, saxitoxin,[4] in the peptide antibiotics capreomycin,[5] viomycin,[6] and tuberactinomycin,[7] in the antifungal agent, stendomycin,[8] and in the alkaloids of *Alchornea javanensis*.[9] Interestingly, all of these compounds contain the guanidine moiety as part of a cyclic system.

Thus it is of interest to prepare guanidines which are suitably functionalized to permit a variety of synthetic manipulations, the most important of which is probably the conversion to cyclic guanidines, retaining some functionality in addition to the guanidino group. This paper describes routes to acyclic and cyclic guanidino diesters, namely, **1** and **2**; the routes are general and



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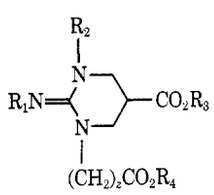

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flexible in design so that such intermediates may find wide synthetic use. Two groups of such esters are described: (1) tosyl-protected guanidino diesters (**1**, R_1 = Ts; **2**, R_1 = Ts) and (2) unprotected guanidino diesters. The tosyl protecting group is very useful in these syntheses, since the possible interference of the strongly alkaline guanidine function is largely eliminated. Also, the facile deprotection of tosylguanidines with anhydrous HF[10,11] makes this an especially suitable protecting group.

Tosyl-Protected Guanidino Diesters.—Any of the six reaction paths a–f can be used to prepare tosyl-protected guanidino diesters.

The first four synthetic routes are based on a variation of the classical Rathke[12] guanidine synthesis, the reaction of an *S*-methylisothiourea with an amine. In our approach the *S*-methylisothiourea is first converted to the more reactive amidinium chloride (*e.g.*, **11**) or carbodiimide (*e.g.*, **7**), since the conditions required for direct conversion of an isothiourea to a guanidine are too drastic for use with sensitive amino esters.

The entire scheme hinges on the availability of the appropriate *S*-methylisothioureas (*e.g.*, **4**, **10**, **16**,) and we have found that such compounds can be generated with ease from *S*,*S*-dimethyl-*N*-*p*-toluenesulfonyliminodithiocarbonimidate (**3**) or from *p*-toluenesulfonylisothiocyanate (**14**). The thiomethyl groups of the former compound were shown[13] to undergo nucleophilic displacement. This displacement reaction was then extended[14] to include the sodium salts of various β-amino acids as in **3** → **4**. The preparation of various sulfonyl isothiocyanates (*e.g.*, **14**) has also been described.[13,15,16]

Reaction path a is useful for the preparation of guanidines of type **8** (**1** in which either R_2 or R_3, or both are H). The intermediate *S*-methylisothiourea **4** can be obtained by direct displacement of a methylthio group of **3** with the sodium salt of an amino acid,[14] a process which requires boiling in ethanol. Such conditions are untenable if an amino acid ester is to be used directly because of competing diketopiperazine formation. Under these conditions *N*-methylamino acids do not displace the methylthio group of **3** and, as a result, path a is limited to the production of guanidines such as **8**.

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(2) C. Lempert, *Chem. Rev.*, **59**, 667 (1959).

(3) A. Furusaki, Y. Tomije, and I. Nitta, *Bull. Chem. Soc. Jap.*, **43**, 3332 (1970), and references cited therein.

(4) J. Wong and H. Rapoport, *J. Amer. Chem. Soc.*, **93**, 7344 (1971).

(5) B. W. Bycroft, D. Cameron, and A. W. Johnson, *J. Chem. Soc. C*, 3040 (1971).

(6) B. W. Bycroft, L. R. Croft, A. W. Johnson, and T. Webb, *J. Chem. Soc., Perkin Trans. 1*, 820 (1972).

(7) H. Yoshioka, T. Aoki, H. Goko, K. Nakatsu, T. Noda, H. Sakakibara, T. Take, A. Nagata, J. Abe, T. Wakamiya, T. Shiba, and T. Kaneko, *Tetrahedron Lett.*, **No. 23**, 2043 (1971).

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(9) N. K. Hart, S. R. Johns, J. A. Lamberton, and R. I. Willing, *Aust. J. Chem.*, **23**, 1679 (1970).

(10) R. H. Mazur and G. Plume, *Experientia*, **24**, 661 (1968).

(11) J. V. Rodricks and H. Rapoport, *J. Org. Chem.*, **36**, 46 (1971).

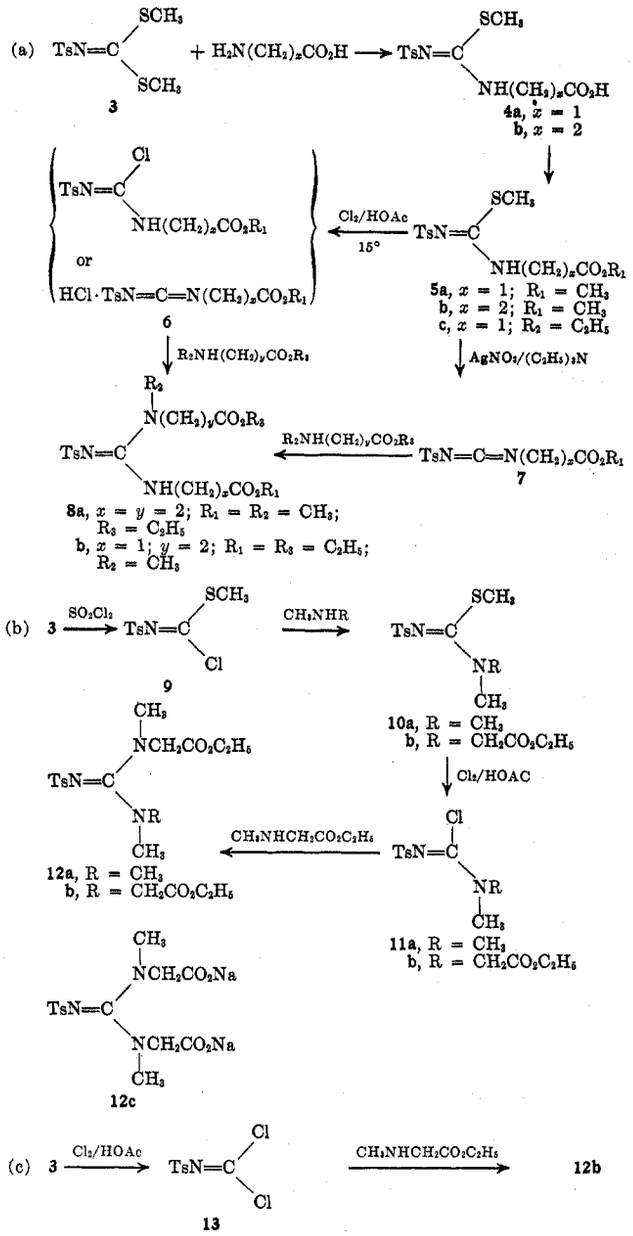
(12) B. Rathke, *Ber.*, **17**, 297 (1884).

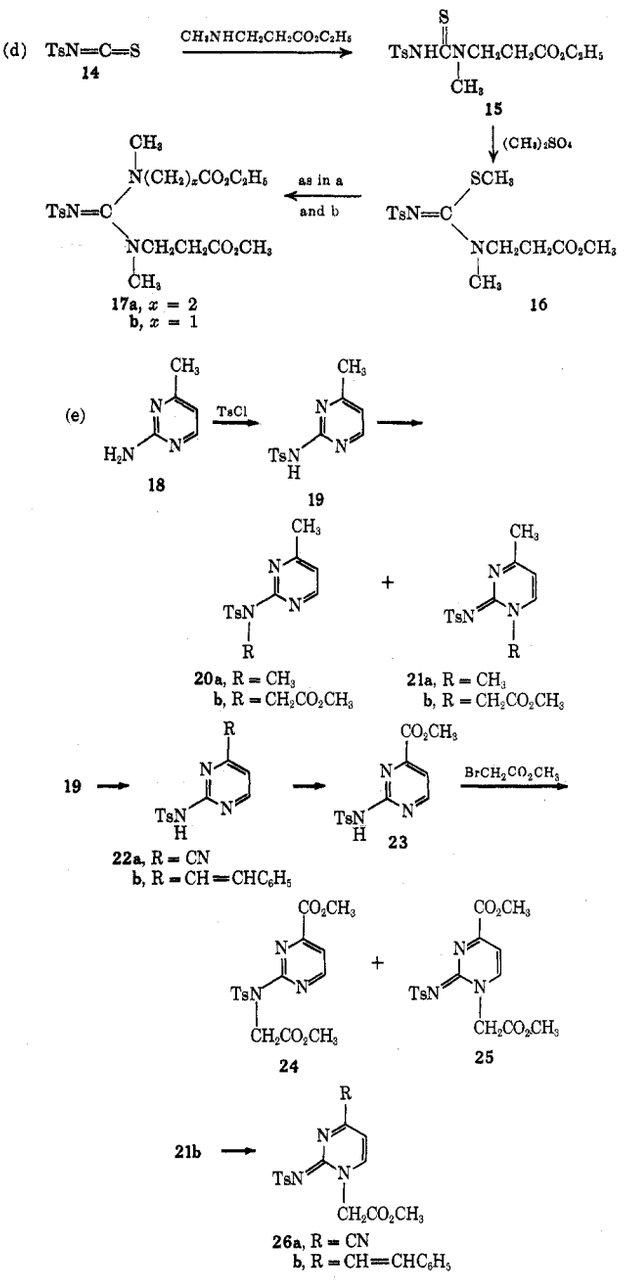
(13) R. Gompper and W. Hagele, *Chem. Ber.*, **99**, 2885 (1966).

(14) J. Gante, *Angew. Chem.*, **19**, 858 (1967).

(15) K. Hartke, *Arch. Pharm. (Weinheim)*, **299**, 174 (1966).

(16) K. Dickore and E. Kuhle, *Angew. Chem., Int. Ed. Engl.*, **4**, 430 (1965)





Esterification of the acid **4** can be effected with either methyl iodide or dimethyl sulfate; if other than a methyl ester is desired, Fischer esterification is successful. Use of the alkylating agents does not cause alkylation of the isothiourea nitrogen. The *S*-methylisothiourea **5**, when treated with $AgNO_3/Et_3N$,[17] is converted to the intermediate sulfonylcarbodiimide **7**; the latter is not isolated but is immediately trapped by the appropriate amino ester to yield the guanidino diester. Alternatively, the sulfonylcarbodiimide salt or chloro amidine **6** can be generated by chlorination of the isothiourea **4**.

Pathway b is based on the conversion of **3** to the monochlorinated compound **9** using sulfuryl chloride as the chlorinating agent.[18] The monochloro compound **9** then undergoes nucleophilic displacement at room temperature with the appropriate amino ester to produce the corresponding *S*-methylisothiourea **10**, which is converted to the guanidino diester using the procedure of path a. Use of the $AgNO_3/Et_3N$ reagent is prohibited in this sequence, and the chloro amidine **11** will be the reactive intermediate.

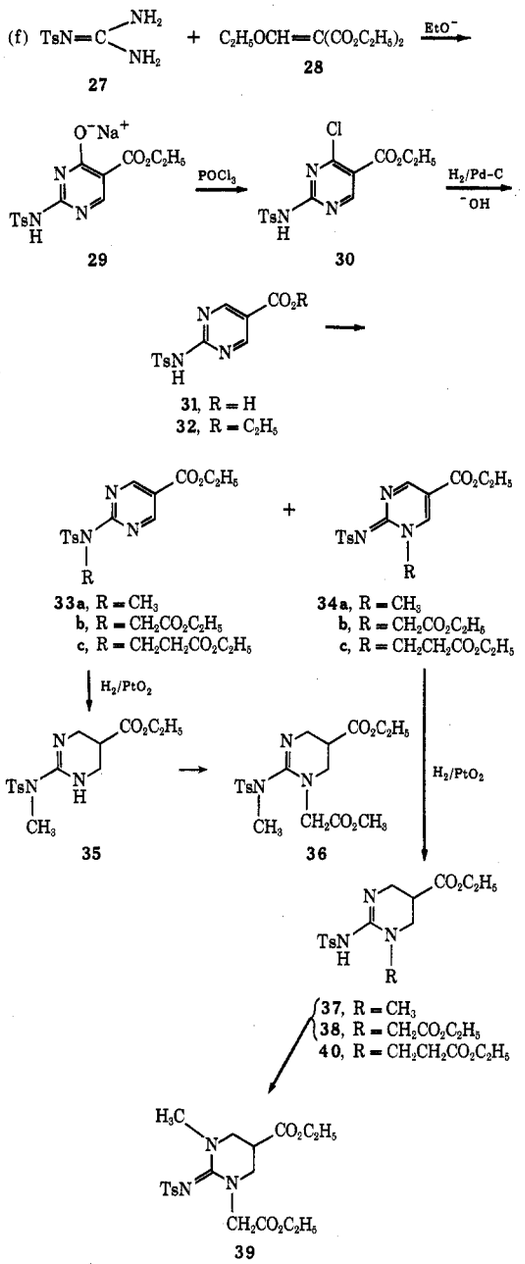
Path c is useful because it is a one-step reaction, although it is limited to the introduction of identical amino ester fragments. *S,S*-Dimethyl-*N*-*p*-toluenesulfonyliminodithiocarbonimidate (**3**) is smoothly converted to *N*-*p*-toluenesulfonylimidocarbonyl chloride (**13**) upon treatment of a glacial acetic acid solution of **3** with Cl_2.[19] The dichloro compound readily reacts with 2 equiv of an amino ester at room temperature or below.

Path d is as flexible as path b; *p*-toluenesulfonylisothiocyanate (**14**) reacts readily with amino esters to afford *N*-tosylthioureas **15**. The thiourea can be converted to an *S*-methylisothiourea by action of an alkyl-

(17) A. F. Ferris and B. A. Schutz, *J. Org. Chem.*, **28**, 71 (1963).

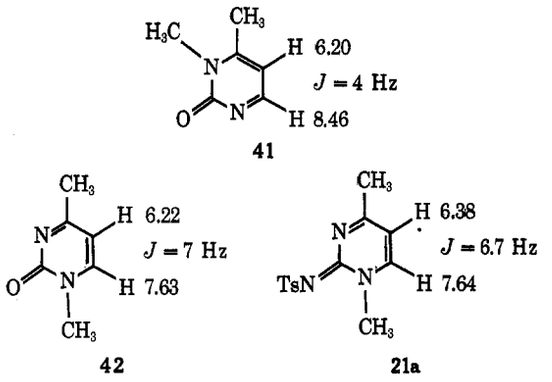
(18) R. Neidlein and W Haussmann, *Angew. Chem., Int. Ed. Engl.*, **4**, 521 (1965).

(19) R. Neidlein and W. Haussmann, *Tetrahedron Lett.*, **No. 22**, 1753 (1965); R. Gompper and R. Kunz, *Chem. Ber.*, **99**, 2900 (1966).



ating agent, although the alkylation process results in transesterification as well (**15** → **16**). Generally path d results in somewhat better yields of *S*-methylisothiourea than can be achieved by path b.

Path e is applicable for the synthesis of tosylguanidines from 2-aminopyrimidines on which exocyclic tosylation with *p*-toluenesulfonyl chloride in pyridine proceeds easily.[20] However, alkylation, contrary to the literature regarding *N*-sulfonylaminopyrimidines,[20] results in both exo (**20**) and endo (**21**) isomers, with no apparent alkylation at N-3. The exo isomer was identified by comparison to an authentic sample prepared unambiguously *via* the Ullman reaction[21] with *N*-methyl-*p*-toluenesulfonamide and 2-chloro-4-methylpyrimidine. Structural assignment of the endo isomer was based upon the nmr comparison of the pyrimidine ring protons with those of the 3,4- and 1,4-dimethyl-2-oxo-pyrimidines,[22,23] **41** and **42**, respectively. The 2-tosylamidopyrimidines could be further substituted by



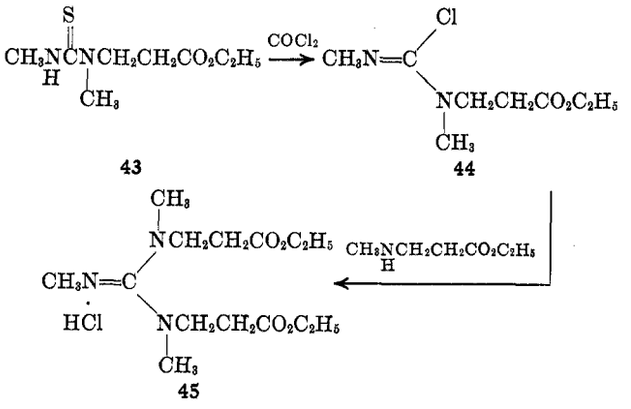
alkylation with various alkyl halides and by oxidation of the C-4 methyl either before or after alkylation.[24,25] Reduction of the pyrimidines would then proceed to yield the desired functionalized tosyl-protected guanidines.[26]

Path f extends the synthesis to 2-aminopyrimidines which cannot be directly tosylated with tosyl chloride. It was found that tosylguanidine readily condenses with diethyl ethoxymethylenemalonate in sodium ethoxide–ethanol to give the salt of the pyrimidin-4-one **29**.[27] This salt, when heated with phosphorus oxychloride, gives the 4-chloropyrimidine **30** in high yield without the presence of the usual tertiary amine.[27c] Reductive dehalogenation[28] followed by esterification yields 2-tosylamido-5-ethoxycarbonylpyrimidine (**32**). Alkylation and ring reductions as described in path e result in various functionalized tosyl-protected cyclic guanidines in which one ester function is at C-5 rather than at C-4. It should be noted that the alkylation of the trialkyl guanidines **37** and **38** occurs predominantly on the endocyclic nitrogen with very little alkylation on the exocyclic tosylated nitrogen.

Unprotected Guanidine Diesters.—The synthesis of unprotected guanidines carrying a diester function is modeled after path d of the tosyl-protected guanidino diester synthesis. Thus, the synthesis depends upon the availability of alkyl isothiocyanates. As an example, methyl isothiocyanate was treated with ethyl 3-*N*-methylaminopropionate to afford the thiourea **43**, which was converted by phosgene[29] to the chloro formamidinium chloride **44**. In this case the base-weakening effect of the sulfonyl group is eliminated, and the

(20) J. P. English, J. H. Clark, R. G. Shephard, H. W. Marson, J. Krapcho, and R. O. Roblin, Jr., *J. Amer. Chem. Soc.*, **68**, 1039 (1946).
(21) M. A. Phillips, *J. Chem. Soc.*, 9 (1941).
(22) D. J. Brown and T. C. Lee, *Aust. J. Chem.*, **19**, 2321 (1966).
(23) D. J. Brown and T. C. Lee, *Aust. J. Chem.*, **21**, 243 (1968).
(24) T. Matsukawa and K. Shirakawa, *J. Pharm. Soc. Jap.*, **72**, 909 (1952).
(25) G. Daves, P. O'Brien, L. Lewis, and C. Cheng., *J. Heterocycl. Chem.*, **1**, 130 (1964).
(26) (a) H. Aft and B. E. Christensen, *J. Org. Chem.*, **27**, 2170 (1962); (b) R. F. Evans, *J. Chem. Soc.*, 2450 (1964); (c) R. F. Evans and J. S. Shannon, *J. Chem. Soc.*, 1406 (1965); (d) B. W. Bycroft, D. Cameron, L. R. Croft, and A. W. Johnson, *Chem. Commun.*, 1301 (1968).
(27) For analogous reactions with diethyl ethoxymethylenemalonate see (a) H. C. Koppel, R. H. Springer, R. K. Robins, and C. Cheng, *J. Org. Chem.*, **27**, 3614 (1962); (b) J. H. Chesterfield, D. T. Hurst, J. W. F. McOmie, and M. S. Tute, *J. Chem. Soc.*, 1001 (1964); (c) E. Peters, J. F. Holland, B. Bryant, H. J. Minnemeyer, C. Hohenstein, and H. Tieckelmann, *Cancer Res.*, **19**, 729 (1959).
(28) R. G. Shepherd, W. E. Taft, and H. M. Krazinski, *J. Org. Chem.*, **26**, 2764 (1961).
(29) For similar reactions see H. Eilingsfeld, G. Naubauer, M. Seefelder, and H. Weidinger, *Chem. Ber.*, **97**, 1232 (1964).

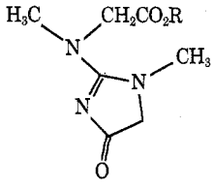
product forms a salt with the HCl released during the reaction. The intermediate **44** was taken to the guanidino diester hydrochloride **45**; also resulting from the



reaction was 1 equiv of amino ester hydrochloride, giving a mixture of water-soluble salts. Advantage can be taken of the great difference in basicity between amino ester salt and guanidino diester salt, and the pair can be separated by ion-exchange chromatography on an acid resin. The 4 *N* acid required to remove the guanidine salt effects ester hydrolysis; however, reesterification of the diacid, using ethanolic HCl, proceeds with ease. The overall yield of final diester **45**, based on thiourea **43** and including ion-exchange chromatography and reesterification, is 52%. Although our work on unprotected guanidino diesters is limited to this single case, it is presumably widely applicable and is based on the availability of alkyl isothiocyanate.

Deprotection of Tosyl-Protected Guanidino Diesters.—The tosyl-protected guanidino diesters are potential intermediates for the synthesis of a variety of functionalized guanidines, the *N*-tosyl group providing protection from the intervention of the strongly alkaline guanidine group in any further chemical manipulations of the diesters. However, attempts to remove the tosyl group by exposure to anhydrous HF, a procedure which has been demonstrated to remove tosyl groups from guanidines quantitatively,[11] yielded the corresponding acylguanidines.

When *N*-tosyl-*N'*,*N''*-dimethyl-*N'*,*N''*-di(ethoxycarbonylmethyl)guanidine (**12b**) was stirred at room temperature for 2 hr in anhydrous HF, detosylation was effected, but in addition the detosylated intermediate underwent cyclization to form the imidazolin-4-one **46a** in very good yield. Likewise, **12a** and the cyclic guanidino diesters **36** and **38–40** gave their respective analogs **47–51** under the same conditions in 30–90% yield. The detosylation of the disodium salt **12c** in HF resulted in the isolation in a 20% yield of the acid **46b**



46a, R = C_2H_5
b, R = H

after ion-exchange chromatography. The ethyl ester **46a** was obtained by Fisher esterification, indicating that both acids and esters experienced cyclization under these conditions. Fisher esterification of **12c** gave only tosylamide and sarcosine ethyl ester. Thus in all examples where the N substituents are either acetate or propionate residues, the use of HF as a detosylating agent leads to imidazolinones or their homologs.

To verify that the cyclization resulted from the detosylation conditions and not during the isolation procedure, *N*-*p*-toluenesulfonyl-*N'*,*N''*,*N''*-trimethyl-*N'*-ethoxycarbonylmethylguanidine (**12a**) and **41** were subjected to the detosylation conditions and, after removal of the HF, the residues were immediately examined by nmr. The spectra indicated that cyclization had occurred to give **52** and **55**, as was evidenced by the absence of the ethyl ester absorption for **52** and the presence of a single ethyl ester for **55**, identical with the spectrum of **55** prepared independently.

The bicyclic series contains both acylamino (**48**) and acylimino (**49–51**) forms of the imidazolinones, thereby permitting a comparison of their properties. The uv absorption maxima (λ_{max} 222–229 nm) and extinction coefficients (ϵ 16,000–20,000) for the obligatory acylimino compounds **46**, **47**, and **50** and the values for the acylamino isomer **48** (λ_{max} 210 nm ϵ 9750) correlate well with the reported values and substantiate the use of uv spectroscopy as a means of differentiating between the two tautomeric forms.[30,31] These data also established the acylimino structure as the preferred tautomer for the labile imidazolinone **49** and tetrahydropyrimidinone **51**.

Although the C-5 hydrogens of the imidazolin-4-ones are potentially exchangeable, little work has been reported other than a single study involving deuterium exchange at pD 9 in which the acylamino tautomers underwent exchange much more rapidly than their acylimino counterparts.[31] The variety of compounds (**46–51**) which we prepared permitted a more detailed study, and their exchange behavior was examined in phosphate buffer solutions at pD's 3, 7, and 10. In addition, compound **50** was examined at pD 1 (D_2SO_4–D_2O) and at pD 13 (NaOD–D_2O).

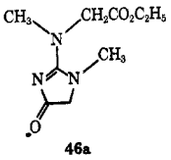
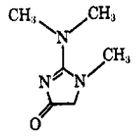
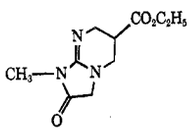
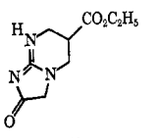
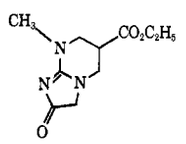
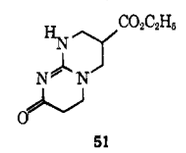
From Table I it is apparent that the tetrahydropyrimidinone **51** undergoes negligible exchange over the pD range observed relative to the imidazolinones. Within the imidazolinone series, exchange for the acylamino compound **48** was more sensitive to pD than were those compounds containing the acylimino group. Generally the rate of exchange increases as one goes to a more acidic pD; indeed, at pD 1, **49** undergoes complete exchange within 5 min. For compound **47**, however, the rate increased upon raising the pD from 7 to 10, which was paralleled by the behavior of **49**; **49** underwent complete deuterium exchange at pD 13 within 5 min. Apparently two mechanisms are involved; however, the one in the lower pD range is of greater interest.

A simple "enolic" mechanism for the acid-catalyzed exchange can be eliminated because it implies comparable rates of exchange for the pyrimidinone **51** as well as for the imidazolinones. That the exchange in-

(30) K. Matsumoto and H. Rapoport, *J. Org. Chem.*, **33**, 552 (1968).
(31) G. L. Kenyon and G. L. Rowley, *J. Amer. Chem. Soc.*, **93**, 5552 (1971).

TABLE I

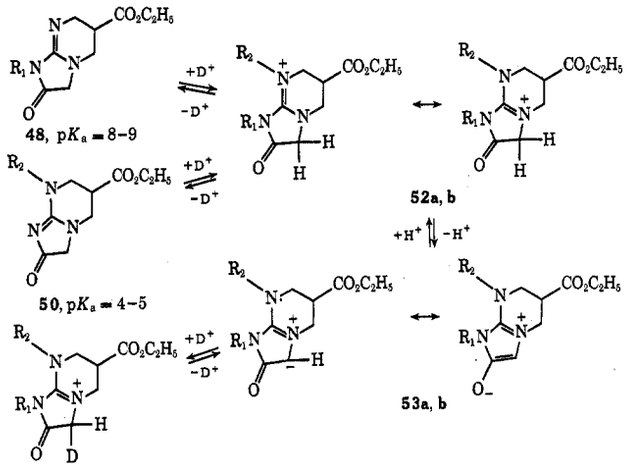
DEUTERIUM EXCHANGES[a] OF SOME IMIDAZOLINONES AND TETRAHYDROPYRIMIDINONES

Compd	Half-life, min pD 3[b]	pD 7[b]	pD 10[b]
 46a	5–10	60	*c*
 47	10–15	90	45
 48	5	20	*d*
 49	115	150	1000
 50	140	1250	2000
 51	1300[e]	1300[e]	1300[e]

[a] Exchange performed in aqueous phosphate buffer solutions. [b] ±0.5 pD. [c] Ester hydrolysis interfered with exchange measurements. [d] Hydrolysis of the imidazoline ring was more rapid than exchange. [e] Less than 5% exchange (detectability limit) had occurred when the experiment was terminated; therefore, this is a lower limit.

creases with decreasing pD indicates the necessity of a protonated intermediate. Such a protonated species **52** is structurally analogous to and isoelectronic with the oxazolin-4-one salts.[32] As with the oxazolinonium compounds, it is not difficult to envision the loss of a proton from C-5 to give a mesoionic intermediate **53** which is analogous to munchnones,[33] sydnones,[34] and other mesoionic compounds.[35] Such an intermediate is not possible with the pyrimidinone because of the additional methylene, and what exchange does occur proceeds *via* a different mechanism.

The difference in exchange behavior between the acylamino and acylimino imidazolinones is readily explained by their pK_a differences. Compound **48** possesses a pK_a of approximately 8–9, whereas the values of the other imidazolinones are in the 4–5 region.[30,31] Therefore, at pD 7, **48** would be greater than 90% protonated while the acylimino imidazolinones are less than 1% protonated. Because exchange requires the protonated species **52**, only **52a** (R_1 = CH_3; R_2 = D) exists in a concentration large enough to yield rapid exchange. As one progresses to pD 3, the rate of exchange for the acylimino imidazolinones increases to a rate comparable to that of the acylamino compound at pD 7, as expected, since the necessary intermediate **52b** (R_1 = D; R_2 = CH_3) now represents approximately 90% of the total concentration. The rate of exchange for **53** at pD **3** is very rapid and is matched by **50** only when the pD is lowered to 1.



In the higher pD region, the exchange mechanism probably involves simply proton removal from C-5 followed by deuteration. Such polar abstraction is reported to be accomplished with triethylamine in the oxazolinone series[33,36,37] and it would seem unlikely that the mechanism would differ significantly with the imidazolinones.

Experimental Section[38]

N-(**Methylmercapto-*N*-*p*-toluenesulfonylcarbonimidoyl)-β-alanine (4b).**—A solution of 0.445 g (5 mmol) of β-alanine, 12.5 ml of ethanol, 5 ml of 1 *N* NaOH solution, and 1.38 g (5 mmol) of *S,S*-dimethyl-*N*-*p*-toluenesulfonyliminodithiocarboimidate (**3**)[13] was heated at reflux for 5.5 hr. Upon cooling in an ice bath, acidification with 5 ml of 1 *N* HCl solution, and standing for 2 days, 1.12 g (71%) of crystals of **4b** formed: mp 114–116°; nmr

(32) E. Brunn, E. Funke, H. Gotthardt, and R. Huisgen, *Chem. Ber.*, **104**, 1562 (1971), and references cited therein.

(33) G. V. Boyd and P. H. Wright, *J. Chem. Soc., Perkin Trans. 1*, 914 (1972).

(34) F. H. C. Stewart, *Chem. Rev.*, **64**, 129 (1964).

(35) W. Baker and W. D. Ollis, *Quart. Rev., Chem. Soc.*, **11**, 15 (1957).

(36) G. V. Boyd and P. H. Wright, *J. Chem. Soc., Perkin Trans. 1*, 909 (1972).

(37) H. Gotthardt, R. Huisgen, and H. O. Bayer, *J. Amer. Chem. Soc.*, **92**, 4340 (1970).

(38) All boiling points and melting points are uncorrected unless otherwise stated. Microanalyses were performed by the Analytical Laboratory, University of California; uv spectra were obtained in absolute ethanol (unless otherwise specified) on a Cary 14 spectrophotometer; infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer. Nmr spectra were recorded on a Varian T-60 or HA-100 spectrophotometer in CDCl$_3$ (unless otherwise specified) using internal TMS or 3-(trimethylsilyl)propanesulfonic acid sodium salt for water-soluble compounds (δ 0). Mass spectra were obtained on a Varian M-66. Thin layer chromatography was done on silica gel and column chromatography was done with Merck silica gel (0.05–0.2 mm) unless specified otherwise.

(CF_3COOH) δ 7.40–8.08 (AB q, 4 H), 3.95 (m, 2 H), 2.97 (t, 2 H), 2.68 (s, 3 H), and 2.48 (s, 3 H).

Anal. Calcd for $C_{12}H_{16}N_2O_4S_2$: C, 45.6; H, 5.1; N, 8.9; S, 20.3. Found: C, 45.4; H, 5.3; N, 8.7; S, 20.2.

***N*-(Methylmercapto-*N*-*p*-toluenesulfonylcarbonimidoyl)-β-alanine Methyl Ester (5b).**—Stirring a solution of 0.250 g (0.79 mmol) of **4b**, 1.12 g (7.90 mmol) of methyl iodide, and 10 ml of methanol overnight at room temperature followed by heating at reflux for 3 hr and removal of methanol yielded 0.16 g (60%) of ester **5b**: mp 125–126°; nmr (CF_3COOH) δ 7.38–7.98 (AB q, 4 H), 3.97 (m, 2 H), 3.85 (s, 3 H), 2.92 (t, 2 H), 2.67 (s, 3 H), and 2.47 (s, 3 H); uv (90% EtOH) λ_{max} 239 nm (ε 19,820).

Anal. Calcd for $C_{13}H_{18}N_2O_4S_2$: C, 47.3; H, 5.5; N, 8.5; S, 19.4. Found: C, 47.3; H, 5.4; N, 8.7; S, 19.3.

***N*-(Methylmercapto-*N*-*p*-toluenesulfonylcarbonimidoyl)glycine Methyl Ester (5a).**—A solution of 0.453 g (1.5 mmol) of *N*-(methylmercapto-*N*-*p*-toluenesulfonylcarbonimidoyl)glycine (**4a**),[14] 0.315 g (1.65 mmol) of tris(2-hydroxypropyl)amine, 0.227 g (1.80 mmol) of dimethyl sulfate, and 20 ml of methanol was boiled for 1 hr. Cooling gave crystals which were recrystallized from methanol to yield 0.44 g (93%) of ester **5a**, mp 119–120°.

Anal. Calcd for $C_{12}H_{16}N_2O_4S_2$: C, 45.6; H, 5.1; N, 8.9; S, 20.3. Found: C, 45.3; H, 5.2; N, 9.0; S, 20.0.

***N*-(Methylmercapto-*N*-*p*-toluenesulfonylcarbonimidoyl)glycine Ethyl Ester (5c).**—The ethyl ester was prepared by boiling a solution of 3.15 g of **4a**[14] in 30 ml of absolute ethanol containing 2 ml of concentrated sulfuric acid. Water (50 ml) was added, the aqueous phase was extracted with benzene, and the benzene layer was washed with aqueous Na_2CO_3 and water, and then dried. Evaporation and crystallization of the residue from ethanol gave ethyl ester **5c**: 2.94 g (87%); mp 119–120°; nmr δ 7.90–7–25 (q, 4 H), 4.18 (d, 2 H), 4.15 (q, 2 H), 2.44 (s, 3 H), 2.40 (s, 3 H), and 1.04 (t, 3 H); mass spectrum *m/e* 330 (M^+), 285 ($M^+ - OC_2H_5$).

Anal. Calcd for $C_{13}H_{18}N_2O_4S_2$: C, 47.3; H, 5.5; N, 8.5; S, 19.4. Found: C, 47.1; H, 5.6; N, 8.6; S, 19.2.

***N*-*p*-Toluenesulfonyl-*N'*-methyl-*N'*-(2-ethoxycarbonylethyl)-*N''*-(2-methoxycarbonylethyl)guanidine (8a).**—To a solution of 0.66 g (2 mmol) of **5b**, 1.05 g (8.0 mmol) of ethyl 3-*N*-methylaminopropionate,[39] and 0.20 g (2 mmol) of Et_3N in 30 ml of acetonitrile, cooled in an ice bath, was added dropwise a solution containing 0.34 g (2 mmol) of $AgNO_3$ in 3 ml of acetonitrile. An immediate yellow precipitate of $AgSCH_3$ formed. The mixture was allowed to warm to room temperature and was stirred overnight. The $AgSCH_3$ was removed by centrifugation, sonicated three times with acetonitrile, and recentrifuged three times. Removal of the acetonitrile gave a red oil, which was placed on a column containing 80 g of silica gel and eluted with 2% CH_3OH–$CHCl_3$. Three 50-ml fractions were initially taken followed by 15 25-ml fractions. Combining fractions 11–16 gave 0.57 g (68%) of the guanidine **8a**: R_f 0.51 with 2% CH_2OH–$CHCl_3$ and 0.65 with 5% CH_3OH–$CHCl_3$ on silica gel; uv λ_{max} 230 nm (ε 15,320); nmr (CF_3COOH) δ 7.95–7.39 (AB q, 4 H), 4.29 (q, 2 H), 3.79 (s, 3 H), 3.74 (m, 4 H), 3.15 (s, 3 H), 2.83 (broad s, 4 H), 2.48 (s, 3 H), 1.28 (t, 3 H).

Anal. Calcd for $C_{18}H_{27}N_3O_6S$: C, 52.3; H, 6.6; N, 10.2; S, 7.8. Found: C, 52.0; H, 6.6; N, 10.1; S, 8.0.

***N*-*p*-Toluenesulfonyl-*N'*-methyl-*N'*-(2-ethoxycarbonylethyl)-*N''*-ethoxycarbonylmethylguanidine (8b).**—To 15 ml of glacial acetic acid cooled in an ice bath and saturated with Cl_2 gas was added 330 mg (1 mmol) of **5c** and the solution was allowed to stir at 14° for 3 hr. The excess Cl_2 was removed *in vacuo* at room temperature and the acetic acid was removed by lyophilization to yield **6** ($x = 1$; $R_1 = C_2H_5$) as a crystalline, colorless solid. This solid was dissolved in 5 ml of acetonitrile, cooled in an ice bath, and treated dropwise with a solution of ethyl 3-*N*-methylaminopropionate (262 mg, 2.0 mmol)[39] in 3 ml of acetonitrile. The solution was allowed to stir for 3 hr at ice-bath temperature and then overnight at room temperature. Removal of the solvent gave a pale yellow oil which was purified by chromatography on a 30-g silica gel column, eluting with 5% CH_3OH–$CHCl_3$. The product, guanidine **8b**, was obtained crystalline from ethanol–ether: 380 mg (92%); mp 104–105°; nmr δ 7.8–7.0 (AB q, 4 H), 4.2–3.8 (q plus d, 6 H, 2-OCH_2– and $NCH_2C{=}O$) 3.50 (t, 2 H, NCH_2–), 2.82 (s, 3 H, NCH_3), 2.43 (t, 2 H, $-CH_2-C{=}O$), 2.28 (s, 3 H, CH_3), 1.08 (t, 6 H, CH_3C); mass spectrum *m/e* 413 (M^+), 368 ($M^+ - OC_2H_5$).

Anal. Calcd for $C_{18}H_{27}N_3O_6S$: C, 52.3; H, 6.6. Found: C, 51.9; H, 6.7.

***N*-(Methylmercaptochloromethylene)-*p*-toluenesulfonimide (9).**—The dithiocarbonimidate **3**, 1.38 g (5.0 mmol), in 20 ml of CCl_4 containing 0.40 ml (5.0 mmol) of SO_2Cl_2 was heated at reflux for 9 hr and then stirred at room temperature overnight. Removal of the solvent and chromatography on silica gel, eluting with $CHCl_3$, gave 0.98 g (68%) of **9**: mp 84–87° (lit.[19] mp 89–90°); nmr δ 7.90–7.25 (AB q, 4 H), 2.48 (s, 6 H).

***N*-*p*-Toluenesulfonyl-*N'*-methyl-*N'*-ethoxycarbonylmethyl-*S*-methylisothiourea (10b).**—*N*-(Methylmercaptochloromethylene)-*p*-toluenesulfonimide (**9**) (0.33 g, 1.2 mmol) was dissolved in 8 ml of acetonitrile, and after cooling in an ice bath, a solution of sarcosine ethyl ester (0.336 g, 2.87 mmol)[40] in 2 ml of acetonitrile was added dropwise. The solution was allowed to stir for 1 hr at 0°, then 40 hr at room temperature. Removal of the solvent and chromatography on 50 g of silica gel, eluting with 2% CH_3OH–$CHCl_3$, gave the isothiourea **10b**: 0.344 g (87%); mg 99–100°; nmr (CF_3COOH), δ 7.91–7.30 (AB q, 4 H), 4.57 (s 2 H), 4.28 (q, 2 H), 3.43 (s, 3 H), 2.54 (s, 3 H), 2.43 (s, 3 H), 1.29 (t, 3 H).

Anal. Calcd for $C_{14}H_{20}N_2O_4S_2$: C, 48.8; H, 5.9; N, 8.1; S, 18.6. Found: C, 48.7; H, 5.8; N, 8.0; S, 18.6.

***N'*,*N'*,*S*-Trimethyl-*N*-*p*-toluenesulfonylcarbonimidate (10a).**—To 6.5 g (25 mmol) of **9** dissolved in 100 ml of acetonitrile and cooled to 0° was added 50 ml of an acetonitrile solution containing 4 ml of dimethylamine. The temperature was maintained at 0° for 3 hr and then allowed to warm to room temperature. After being stirred overnight, the solution was stripped to dryness and the residue was purified by chromatography on silica gel using 2% CH_3OH–$CHCl_3$ as the eluent. The imidate **10a** was obtained in 84% yield (5.6 g): mp 55–57°; nmr δ 7.52 (AB q, 4 H), 3.20 (s, 6 H), 2.42 (s, 3 H), 2.38 (s, 3 H).

Anal. Calcd for $C_{11}H_{16}N_2O_2S_2$: C, 48.5; H, 5.9; S, 23.5. Found: C, 48.5; H, 5.8; S, 23.8.

***N*-*p*-Toluenesulfonyl-*N'*,*N'*,*N''*-trimethyl-*N''*-ethoxycarbonylmethylguanidine (12a).**—Glacial acetic acid (100 ml) saturated with Cl_2 at 0° was treated dropwise with stirring with 6.36 g (18.6 mmol) of **10a** in 50 ml of glacial acetic acid. The solution was stirred at 5–10° for 2 hr and the solvent and Cl_2 were removed by aspiration. To the residue of **11a** dissolved in 100 ml of acetonitrile and cooled to 0° was added over 10 min, with rapid stirring, 4.40 g (37.6 mmol) of sarcosine ethyl ester dissolved in 25 ml of acetonitrile. After being allowed to warm to room temperature, the reaction mixture was stirred overnight. The solvent was removed by aspiration and the residue was chromatographed on silica gel to yield the product **12a**: 3.8 g (11.2 mmol, 60%); mp 121–122°; nmr δ 7.50 (AB q, 4 H), 4.12 (s, 2 H), 4.03 (q, 2 H), 3.04 (s, 6 H), 2.94 (s, 3 H), 2.36 (s, 3 H), 1.23 (t, 3 H); uv λ_{max} 237 nm.

Anal. Calcd for $C_{15}H_{23}N_3O_4S$: C, 52.8; H, 6.8; N, 12.3. Found: C, 52.6; H, 6.8; N, 12.2.

***N*-*p*-Toluenesulfonyl-*N'*,*N''*-dimethyl-*N'*,*N''*-di(ethoxycarbonylmethyl)guanidine (12b). A.**—To 12 ml of glacial acetic acid, cooled in an ice bath and saturated with Cl_2, was added dropwise a solution containing 0.27 g (0.78 mmol) of isothiourea **10b** dissolved in 3 ml of glacial acetic acid. The slush was stirred for 2 hr at 14°, the excess Cl_2 was removed by aspiration, and the acetic acid was removed by lyophilization. The resulting yellow oil **11b** was sonicated with three 5-ml portions of petroleum ether (bp 30–60°), dissolved in 5 ml of acetonitrile, and cooled in an ice bath. A solution containing 0.227 g (1.94 mmol) of sarcosine ethyl ester was added dropwise to the cold solution, which was then allowed to stir for 3 hr at 0° and overnight at room temperature. Removal of the solvent gave an oil which was chromatographed on silica gel (30 g), eluting with 2% CH_3OH–$CHCl_3$. A 0.181-g (56.5%) yield of guanidine **14b** was obtained: mp 82–83°; nmr δ 7.92–7.08 (AB q, 4 H), 4.25 (s, 4 H), 4.09 (q, 4 H), 3.06 (s, 6 H), 2.37 (s, 3 H), 1.20 (t, 6 H).

Anal. Calcd for $C_{18}H_{27}N_3O_6S$: C, 52.3; H, 6.6; N, 10.2; S, 7.8. Found: C, 52.5; H, 6.6; N, 10.0; S, 7.7.

B.—To an ice-cooled solution of 1.76 g (7 mmol) of *N*-*p*-toluenesulfonylimidocarbonyl chloride (**13**)[19] in 25 ml of acetonitrile was added dropwise over 40 min a solution of 3.44 g (29.4 mmol) of sarcosine ethyl ester in 5 ml of acetonitrile. The reaction solution was allowed to stir at 0° for 2 hr, then overnight at room temperature. Removal of the solvent *in vacuo* and chro-

(39) R. W. Holley and A. D. Holley, *J. Amer. Chem. Soc.*, **71**, 2124 (1949).

(40) W. Haudt, *Z. Physiol. Chem.*, **146**, 286 (1925).

matography of the residue on silica gel, eluting with 2% CH_3OH–$CHCl_3$, gave **12b** in 75% yield.

***N*-*p*-Toluenesulfonyl-*N'*,*N''*-dimethyl-*N'N''*-di(carboxymethyl)guanidine Disodium Salt (12c).**—A suspension of 2.2 g of **12b** and 235 ml of 0.05 *N* NaOH (dioxane–water) was heated at 70° and stirred overnight. Removal of the solvent by lyophilization gave 2.8 g of a crude product which was digested in hot ethanol, cooled, and filtered to give the purified disodium salt **12c**: nmr (D_2O) δ 7.50 (AB q, 4 H), 3.88 (s, 4 H), 3.00 (s, 6 H), 2.40 (s, 3 H); uv λ_{max} 240 nm.

Anal. Calcd for $C_{14}H_{17}N_3O_6SNa_2$: N, 10.4. Found: N, 10.1.

***N*-*p*-Toluenesulfonyl-*N'*-methyl-*N'*-(2-ethoxycarbonylethyl)-thiourea (15).**—*p*-Toluenesulfonyl isothiocyanate (**14**)[16] (2.13 g, 10 mmol), dissolved in 3.5 ml of ether and cooled in an ice bath, was treated dropwise with a solution containing 1.31 g (10 mmol) of ethyl β-*N*-methylaminopropionate dissolved in 4 ml of ether. The mixture was stirred for 2 hr at 0° and 3 hr at room temperature, then filtered to give a quantitative yield of thiourea **15**: mp 122–123° after recrystallization from benzene–ether; nmr (CF_3COOH) δ 7.94–7.28 (AB q, 4 H), 4.24 (q, 2 H), 4.02 (t, 2 H), 3.30 (s, 3 H), 2.88 (t, 2 H), 2.43 (s, 3 H), 1.30 (t, 3 H).

Anal. Calcd for $C_{14}H_{20}N_2O_4S_2$: C, 48.8; H, 5.9; N, 8.1; S, 18.6. Found: C, 48.6; H, 5.8; N, 8.3; S, 18.8.

***N*-*p*-Toluenesulfonyl-*N'*-methyl-*N'*-(2-methoxycarbonylethyl)-*S*-methylisothiourea (16).**—The thiourea **15**, 0.67 g (2 mmol), 0.42 g (2.2 mmol) of tris(2-hydroxypropyl)amine, 0.3 g (2.4 mmol) of dimethyl sulfate, and 4 ml of methanol were heated at reflux for 1 hr. Evaporation of the methanol and chromatography of the residue on silica gel, eluting with 2% CH_3OH–$CHCl_3$, gave the *S*-methylisothiourea **16**: mp 47–48°; R_f 0.59 on silica gel, eluting with 2% MeOH–$CHCl_3$; nmr (CF_3COOH) δ 7.98–7.38 (AB q, 4 H), 3.94 (m, 2 H), 3.83 (s, 3 H), 3.49 (s, 3 H), 2.96 (t, 2 H), 2.71 (s, 3 H), 2.48 (s, 3 H).

Anal. Calcd for $C_{14}H_{20}N_2O_4S_2$: C, 48.8; H, 5.9; N, 8.1; S, 18.6. Found: C, 49.0; H, 6.0; N, 8.2; S, 18.8.

***N*-*p*-Toluenesulfonyl-*N'*,*N''*-dimethyl-*N'*-(2-ethoxycarbonylethyl)-*N''*-(2-methoxycarbonylethyl)guanidine (17a).**—The *S*-methylisothiourea **16** (1.0 g, 2.9 mmol) dissolved in 2 ml of glacial acetic acid was added dropwise to 15 ml of glacial acetic acid saturated with Cl_2. Following the addition, Cl_2 was again passed into the slush until saturation was achieved. The solution was allowed to stir at 14° for 2 hr, the excess Cl_2 was removed *in vacuo*, and the glacial acetic acid was removed by lyophilization. The residual oil was sonicated with three 5-ml portions of petroleum ether (bp 30–75°), dissolved in 5 ml of acetonitrile, and cooled in an ice bath. To this cold solution was added dropwise an acetonitrile solution containing 0.76 g (5.80 mmol) of ethyl β-*N*-methylaminopropionate. The clear solution was allowed to stir for 3 hr in an ice bath and then overnight at room temperature. Removal of the solvent and purification of the residue *via* a silica gel column, eluting with 4% CH_3OH–$CHCl_3$, gave 0.472 g (38%) of guanidine **17a** as an oil: R_f 0.56 on silica gel with 4% CH_3OH–$CHCl_3$; nmr (CF_3COOH) δ 8.02–7.43 (AB q, 4 H), 4.28 (q, 2 H), 3.82 (s, 3 H), 3.60–3.92 (m, 4 H), 3.18 (s, 6 H), 2.89 (t, 4 H), 2.49 (s, 3 H), 1.30 (t, 3 H).

Anal. Calcd for $C_{19}H_{29}N_3O_6S$: C, 53.4; H, 6.8; N, 9.8; S, 7.5. Found: C, 53.0; H, 6.6; N, 9.8; S, 7.3.

***N*-*p*-Toluenesulfonyl-*N'*,*N''*-dimethyl-*N'*-(ethoxycarbonylmethyl)-*N''*-(2-methoxycarbonylethyl)guanidine (17b).**—The experimental procedure described above was followed in detail employing the following quantities: *N*-*p*-toluenesulfonyl-*N'*-methyl-*N'*-(2-methoxycarbonylethyl)-*S*-methylisothiourea (**16**), 0.82 g (2.39 mmol); sarcosine ethyl ester, 0.56 g (4.8 mmol). The yield was 0.76 g (77%) of guanidine **17b** as an oil: nmr (CF_3COOH) δ 7.99–7.48 (AB q, 4 H), 4.39 (s, 2 H), 4.33 (q, 2 H), 3.84 (s, 3 H), 3.80–3.60 (m, 2 H), 3.29 (s, 3 H), 3.25 (s, 3 H), 3.08–2.08 (m, 2 H), 2.52 (s, 3 H), 1.33 (t, 3 H).

Anal. Calcd for $C_{18}H_{27}N_3O_6S$: C, 52.3; H, 6.6; N, 10.2; S, 7.8. Found: C, 51.9; H, 6.4; N, 10.0: S, 7.5.

2-*p*-Toluenesulfonamido-4-methylpyrimidine (19).—*p*-Toluenesulfonyl chloride (3.80 g, 20 mmol) was added gradually to a solution of 2-amino-4-methylpyrimidine (**18**, 1.08 g, 10 mmol)[41] in 5 ml of pyridine. After stirring at 60° for 2.5 hr, 4 ml of 5 *N* sodium hydroxide was added, the mixture was evaporated to dryness, and the residue was digested in water, cooled, and filtered. Washing with water and crystallization from ethanol gave 1.98 g (76%) of 2-*p*-toluenesulfonamido-4-methylpyrimidine: mp 230–232°; nmr δ 8.41 (d, 1 H), 8.01 (d, 2 H), 7.08 (d, 2 H), 6.66 (d, 1 H), 2.35 (s, 6 H); ir (KBr) 6.28, 6.39 μ; uv λ_{max} 264 nm (ε 4080), 232 (15,600), 218 (15,400).

Anal. Calcd for $C_{12}H_{13}N_3O_2S$: C, 54.8; H, 5.0; N, 16.0. Found: C, 54.8; H, 5.0; N, 15.8.

Alkylation of 2-*p*-Toluenesulfonamido-4-methylpyrimidine (19).—The sodium salt of **19** was generated by the addition of an ethanolic solution of the pyrimidine (1 mol) to a sodium ethoxide (1.05 mol)–ethanol solution, and the cooled suspension was evaporated to dryness. The residue was dissolved in DMSO, a 10% excess of the alkylating agent was added, and the reaction mixture was stirred at room temperature for 2–10 hr, followed by removal of the DMSO at reduced pressure. The residue was partitioned between water and chloroform, and the organic phase was chromatographed employing $CHCl_3$ and 5% C_2H_5OH–$CHCl_3$ as eluents to achieve exo and endo isomer separation. The exo isomers were eluted with chloroform, after which the endo isomers could be quickly eluted with 5% C_2H_5OH–$CHCl_3$, the overall yield of the isomers ranging from 70 to 80%.

2-(*N*-Methyl-*p*-toluenesulfonamido)-4-methylpyrimidine (20a) (yield 52%) had mp 62–63°; nmr δ 8.24 (d, 1 H, J = 4.9 Hz), 7.93 (d, 2 H), 7.23 (d, 2 H), 6.68 (d, 1 H, J = 4.9 Hz), 3.66 (s, 3 H), 2.35 (s, 6 H); ir ($CHCl_3$) 6.34, 6.43 μ; uv λ_{max} 264 nm (ε 4860), 223 (19,800).

Anal. Calcd for $C_{13}H_{15}N_3O_2S$: C, 56.3; H, 5.5; N, 15.2. Found: C, 56.3; H, 5.4; N, 15.2.

1,4-Dimethyl-2-*p*-toluenesulfonimidopyrimidine (21a) (yield 18%) had mp 178–181°; nmr δ 7.89 (d, 2 H), 7.88 (d, 1 H, J = 6.6 Hz), 7.16 (d, 2 H), 6.37 (d, 1 H, J = 6.6 Hz), 3.63 (s, 3 H), 2.40 (s, 3 H), 2.34 (s, 3 H); ir (KBr) 6.15, 6.50 μ; uv λ_{max} 318 nm (ε 4330), 252 (20,900), 223 (12,700).

Anal. Calcd for $C_{13}H_{15}N_3O_2S$: C, 56.3; N, 5.5; N, 15.2. Found: C, 53.4; H, 5.5; N, 14.9.

2-(*N*-Methoxycarbonylmethyl-*p*-toluenesulfonamido)-4-methylpyrimidine (20b) (yield 28%) had mp 120–122°; nmr δ 8.15 (d, 1 H, J = 5.3 Hz), 8.07 (d, 2 H), 7.23 (d, 2 H), 6.65 (d, 1 H, J = 5.3 Hz), 4.98 (s, 2 H), 3.72 (s, 3 H), 2.35 (s, 6 H); ir ($CHCl_3$) 5.67, 6.31, 6.42 μ; uv λ_{max} 265 (s), 222 nm.

Anal. Calcd for $C_{15}H_{17}N_3O_4S$: C, 53.7; H, 5.1; N, 12.5. Found: C, 53.6; H, 5.0; N, 12.4.

1-Methoxycarbonylmethyl-2-*p*-toluenesulfonimido-4-methyl-1,2-dihydropyrimidine (21b) (yield 52%) had mp 163–164°; nmr (DMSO-d_6) δ 8.15 (d, 1 H, J = 6.7 Hz), 7.68 (d, 2 H), 7.27 (d, 2 H), 6.68 (d, 1 H, J = 6.7 Hz), 4.83 (s, 2 H), 3.67 (s, 3 H), 2.30 (s, 6 H); ir (KBr) 5.72, 6.15, 6.49 μ; λ_{max} 316, 245, 216 nm.

Anal. Calcd for $C_{15}H_{17}N_3O_4S$: C, 53.7; H, 5.1; N, 12.5. Found: C, 53.7; H, 5.2; N, 12.5.

Oxidation of 4-Methylpyrimidines 19 and 21b. 2-*p*-Toluenesulfonamido-4-cyanopyrimidine (22a).—To a stirring solution of 8.10 g (31 mmol) of 2-tosylamido-4-methylpyrimidine (**19**) in concentrated hydrochloric–acetic acid (1:9) was added rapidly sodium nitrite (3.7 g, 55 mmol). The reaction mixture was stirred at room temperature for 2 hr and the solid which formed was removed by filtration, washed with water, and dried *in vacuo* to yield 6.95 g (25.4 mmol, 82%) of **22a**: mp 201–203°; nmr (DMSO-d_6) δ 8.58 (d, 1 H, J = 5 Hz), 7.98 (d, 2 H), 7.43 (d, 1 H, J = 5 Hz), 7.38 (d, 2 H), 2.35 (s, 3 H); ir (KBr) 6.38 μ.

2-*p*-Toluenesulfonamido-4-methoxycarbonylpyrimidine (23).—Concentrated sulfuric acid (1.8 ml, 32 mmol) was added to a mixture of **22a** (274 mg, 1.00 mmol) and 10 ml of methanol. After the mixture was heated at reflux for 72 hr, the solid which remained was removed by filtration, washed with methanol, and dried to yield 142 mg (0.46 mmol, 46%) of the ester **23**: mp 236–238°; nmr (DMSO-d_6) δ 8.70 (d, 1 H, J = 5.0 Hz), 7.95 (d, 2 H), 7.51 (d, 1 H, J = 5 Hz), 7.33 (d, 2 H), 3.92 (s, 3 H), 2.37 (s, 3 H); ir (KBr) 5.37, 6.37 μ; uv λ_{max} 297 nm (ε 2930), 275 (2090), 235 (17,600), 222 (15,600).

Anal. Calcd for $C_{13}H_{13}N_3O_4S$: C, 50.8; H, 4.3. Found: C, 50.6; H, 4.1.

2-*p*-Toluenesulfonamido-4-β-styrylpyrimidine (22b).—2-Tosylamido-4-methylpyrimidine (**19**, 1.33 g, 5 mmol), benzaldehyde (1 ml), glacial acetic acid (3 ml), and concentrated hydrochloric acid (1 ml) were heated at reflux for 12 hr. The reaction solution was concentrated and the brown gum which remained was triturated with acetone to give 1.19 g (3.4 mmol, 68%) of pure **22b**, mp 263–265°.

Anal. Calcd for $C_{19}H_{17}N_3O_2S$: C, 64.9; N, 4.9; N, 12.0. Found: C, 64.8; H, 4.7; N, 12.1.

(41) D. M. Burness, *J. Org. Chem.*, **21**, 97 (1956).

1-Methoxycarbonylmethyl-2-*p*-toluenesulfonimido-4-cyano-1,2-dihydropyrimidine (26a).—To 671 mg (2.0 mmol) of 1-methoxycarbonylmethyl-2-tosylimido-4-methylpyrimidine (**21b**) in glacial acetic acid were added sequentially with stirring concentrated hydrochloric acid (0.5 ml) and sodium nitrite (221 mg, 3.2 mmol). The solution was stirred at room temperature for 1.5 hr and the solid which formed was removed by filtration, washed with water, and dried to give 550 mg (1.6 mmol, 80%) of **26a**: mp 199–199.5°; nmr (DMSO-d_6) δ 8.57 (d, 1 H, J = 6.8 Hz), 7.80 (d, 2 H), 7.27 (d, 1 H, J = 6.8 Hz), 7.21 (d, 2 H), 4.94 (s, 2 H), 3.70 (s, 3 H), 2.33 (s, 3 H); ir (KBr) 5.72, 6.18, 6.48 μ; uv λ_{max} 365 nm (ϵ 3200), 253 (19,700), 224 (18,800); mass spectrum m/e 282 ($M^+ - 64$), 281 ($M^+ - 65$).

1-Methoxycarbonylmethyl-2-*p*-toluenesulfonimido-4-β-styryl-1,2-dihydropyrimidine (26b).—A solution consisting of **21b** (6.68 g, 20 mmol), benzaldehyde (15 ml), and acetic acid (60 ml) was heated at reflux for 18 hr. The solvent was removed by distillation, the residue was triturated with ethyl acetate, and the precipitate was collected by filtration, washed with ethyl acetate, and recrystallized from ethyl acetate–methanol to give 5.95 g (14 mmol, 70%) of **26b**: mp 180–182°; nmr (DMSO-d_6) δ 8.28 (d, 1 H, J = 7 Hz), 7.18–7.82 (11 H), 6.97 (d, 1 H, J = 7 Hz), 4.90 (s, 2 H), 3.73 (s, 3 H), 2.30 (s, 3 H); ir (KBr) 5.72, 6.22, 6.55 μ; uv λ_{max} 343 nm (ϵ 23,800), 246 (16,700), 225 (17,100).

Anal. Calcd for $C_{22}H_{21}N_3O_4S$: C, 62.4; H, 5.0; N, 9.9. Found: C, 62.2; H, 5.0; N, 10.1.

Alkylation of 2-*p*-Toluenesulfonamido-4-methoxycarbonylpyrimidine (23).—To a hot solution of 0.90 g (2.9 mmol) of **23** in methanol was added a solution of sodium methoxide (69 mg of sodium dissolved in methanol). The resulting solution was evaporated and the residue was dissolved in DMSO. Methyl bromoacetate (2.9 mmol) was added and the reaction mixture was stirred at room temperature for 5 hr. The solvent was removed *in vacuo*, the residue was partitioned between $CHCl_3$ and H_2O, the organic layer was washed twice with H_2O, dried, and concentrated, and the concentrate was chromatographed on silica gel. Elution with $CHCl_3$ gave the exo and endo isomers in 40 and 30% yields, respectively. The exo isomer **24** had mp 118–120°; nmr δ 8.56 (d, 1 H), 8.5 (d, 2 H), 7.48 (d, 1 H), 7.23 (d, 2 H), 5.03 (s, 2 H), 3.99 (s, 3 H), 3.75 (s, 3 H), 2.40 (s, 3 H); ir ($CHCl_3$) 5.73, 6.38 μ; uv λ_{max} 295, 276, 231 (s), 222 nm. The endo isomer **25** had mp 145–148°; nmr δ 8.05 (d, 1 H), 8.00 (d, 2 H), 7.21 (d, 2 H), 7.13 (d, 1 H), 4.90 (s, 2 H), 3.98 (s, 3 H), 3.74 (s, 3 H), 2.38 (s, 3 H); ir (KBr) 5.78, 6.18, 6.49 μ; uv λ_{max} 360, 252.5, 222 nm.

Anal. Calcd for $C_{16}H_{17}N_3O_6S$: C, 50.7; H, 4.5; N, 11.1. Found: C, 50.4; H, 4.8; N, 10.9.

Sodium 2-*p*-Toluenesulfonamido-4-oxo-5-ethoxycarbonylpyrimidinate (29).—Tosylguanidine (**27**, 118.0 g, 0.56 mol) was added to 700 ml of 0.97 N sodium ethoxide in ethanol; the mixture was brought to reflux and diethyl ethoxymethylenemalonate (**28**, 142.5 g, 0.66 mol) was added over a 20-min period. After heating at reflux for 12 hr, the mixture was cooled and filtered. The precipitate was washed with ethanol and dried to give 192.1 g (0.54 mol, 96.4%) of the pale yellow salt **29**: mp 347–349° dec; nmr (DMSO-d_6) δ 8.25 (s, 1 H), 7.70 (d, 2 H), 7.20 (d, 2 H), 4.10 (q, 2 H), 2.32 (s, 3 H), 1.20 (t, 3 H); ir (KBr) 5.80, 6.43, 6.53 μ.

2-*p*-Toluenesulfonamido-4-chloro-5-ethoxycarbonylpyrimidine (30).—To 100 g (0.28 mol) of the sodium salt **29** was added slowly 1 l. of phosphorus oxychloride. The mixture was gradually warmed and maintained at 110° for 5 hr. The solvent was removed *in vacuo*, the residue was partitioned between ice water and chloroform, and the organic layer was washed twice with water, dried, and evaporated to yield 95.0 g (0.27 mol, 96%) of the chloropyrimidine **30**, recrystallized from 2-propanol: mp 183–185°; nmr δ 8.85 (s, 1 H), 7.98 (d, 2 H), 7.25 (d, 2 H), 4.35 (q, 2 H), 2.42 (s, 3 H), 1.37 (t, 3 H); ir (KBr) 5.75, 5.80, 6.32 μ; uv λ_{max} 254, 230 nm.

Anal. Calcd for $C_{14}H_{14}N_3O_4SCl$: C, 47.3; H, 4.0; N, 11.8. Found: C, 47.2; H, 3.9; N, 11.8.

2-*p*-Toluenesulfonamido-5-carboxypyrimidine (31).—To 30 ml of 0.67 N sodium hydroxide were added 2.47 g (7.0 mmol) of **30** and 0.43 g of 10% palladium on carbon. The mixture was shaken for 2 hr on a Parr hydrogenator, by which time hydrogen uptake had ceased. The catalyst was removed by filtration, the carboxylic acid was precipitated by acidification with hydrochloric acid, and the white precipitate was collected and crystallized from 2-propanol to give 2.0 g (6.8 mmol, 97%) of **31**: mp 300–303° dec; nmr (DMSO-d_6) δ 8.85 (s, 2 H), 7.88 (d, 2 H), 7.32 (d, 2 H), 2.37 (s, 3 H); ir (KBr) 5.68, 6.26 μ; uv λ_{max} 248, 228 nm.

Anal. Calcd for $C_{12}H_{11}N_3O_4S$: C, 49.1; H, 3.8; N, 14.3. Found: C, 48.9; H, 3.9; N, 14.3.

2-*p*-Toluenesulfonamido-5-ethoxycarbonylpyrimidine (32).—2-Tosylamido-5-carboxypyrimidine (**31**, 27.7 g, 95 mmol) was heated at reflux in 100 g of thionyl chloride until hydrogen chloride evolution ceased. The solvent was removed by distillation, absolute ethanol was added, and the mixture was heated at reflux for 4 hr. The precipitate which formed upon cooling was collected, a second crop which formed in the filtrate was added, and the combined ethyl ester **32**, 25.4 g (79 mmol, 83%), one spot by tlc, was recrystallized from 2-propanol: mp 186–187°; nmr δ 9.13 (s, 2 H), 7.98 (d, 2 H), 7.27 (d, 2 H), 4.38 (q, 2 H), 2.40 (s, 3 H), 1.37 (t, 3 H); ir (KBr) 5.78, 6.25 μ; uv λ_{max} 252, 228 nm.

Anal. Calcd for $C_{14}H_{15}N_3O_4S$: C, 52.3; H, 4.7; N, 13.1. Found: C, 52.3; H, 4.7; N, 12.8.

Exo and Endo *N*-Methyl Isomers 33a and 34a.—To a hot suspension of 2-tosylamido-5-ethoxycarbonylpyrimidine (**32**, 22.8 g, 7 mmol) in absolute ethanol (500 ml) was added 100 ml of 0.8 N sodium ethoxide–ethanol. After heating for 15 min, the suspension was evaporated to dryness, the sodium salt was dissolved in 250 ml of DMSO, methyl iodide (7 ml) was added, and the solution was stirred at room temperature for 10 hr. The solvent was removed *in vacuo*, the residue was partitioned between water and chloroform, and the organic phase was washed twice with water, dried, evaporated, and chromatographed, the exo isomer **33a** being eluted with $CHCl_3$ (11.3 g, 34.5 mmol, 49%) and the endo isomer **34a** with 3% C_2H_5OH–$CHCl_3$ (10.6 g, 31.8 mmol, 45%).

Exo isomer 33a had mp 100–101; nmr δ 8.97 (s, 2 H), 7.93 (d, H), 7.25 (d, 2 H), 4.35 (q, 2 H), 3.72 (s, 3 H), 2.38 (s, 3 H), 1.35 (t, 3 H); ir ($CHCl_2$) 5.82, 6.28 μ; uv λ_{max} 260 nm (ϵ 21,800), 231.5 (14,800).

Anal. Calcd for $C_{15}H_{17}N_3O_4S$: C, 53.7; H, 5.1; N, 12.5. Found: C, 53.5; H, 5.0; N, 12.5.

Endo isomer 34a had mp 223–225°; nmr δ 8.83 (d, 1 H, 1.3 Hz), 8.50 (d, 1 H, 1.3 Hz), 7.80 (d, 2 H), 4.27 (q, 2 H), 3.68 (s, 3 H), 2.33 (s, 3 H), 1.30 (t, 3 H); ir ($CHCl_3$) 5.82, 6.11 μ; uv λ_{max} 323 nm (ϵ 3100), 275 (33,700), 223 (17,200).

Anal. Calcd for $C_{15}H_{17}N_3O_4S$: C, 53.7; H, 5.1; N, 12.5. Found: C, 53.6; H, 5.2; N, 12.7.

Exo and Endo Ethoxycarbonylmethyl Isomers 33b and 34b.—The same procedure as above, substituting ethyl bromoacetate for methyl iodide, was used on a 2.0-mmol scale to give 30 mg (0.08 mmol, 4%) of the exo isomer **33b** and 69 mg (1.7 mmol, 85%) of the endo isomer **34b**.

Exo isomer 33b had mp 122–124° from 2-propanol; nmr δ 8.85 (s, 2 H), 7.98 (d, 2 H), 7.18 (d, 2 H), 4.97 (s, 2 H), 4.32 (q, 2 H), 4.20 (q, 2 H), 2.38 (s, 3 H), 1.35 (t, 3 H), 1.27 (t, 3 H); ir ($CHCl_3$) 5.69, 5.79, 6.24 μ; uv λ_{max} 253, 234 nm.

Anal. Calcd for $C_{18}H_{21}N_3O_6S$: C, 53.1; H, 5.2; N, 10.3. Found: C, 53.0; H, 5.1; N, 10.3.

Endo Isomer 34b was an oil: nmr δ 8.93 (d, 1 H, J = 3 Hz), 8.38 (d, 1 H, J = 3 Hz), 7.77 (d, 2 H), 4.77 (s, 2 H), 4.32 (q, 2 H), 4.20 (q, 2 H), 2.37 (s, 3 H), 1.33 (t, 3 H), 1.23 (t, 3 H); ir ($CHCl_3$) 5.70, 5.79, 6.08, 6.41 μ; uv λ_{max} 325, 273, 224 nm.

Anal. Calcd for $C_{18}H_{21}N_3O_6S$: C, 53.1; H, 5.2; N, 10.3. Found: C, 53.0; H, 5.1; N, 10.3.

Exo and Endo 2-Ethoxycarbonylethyl Isomers 33c and 34c.—To 90 ml of DMSO was added 30.0 g (87.5 mmol) of sodium 2-tosylimido-5-ethoxycarbonylpyrimidinate, prepared as above and collecting only the salt which precipitated, and 17.5 g (97 mmol) of ethyl β-bromopropionate, and the reaction mixture was stirred at room temperature for 6 hr. The solvent was evaporated, leaving a residue which was digested with chloroform. The filtered chloroform digest was extracted twice with 50-ml portions of 2 N sodium hydroxide and once with water. Acidification of the combined alkaline and aqueous extracts gave 20.8 g (71 mmol, 81%) of recovered starting pyrimidine as its carboxylic acid. Drying and evaporating the chloroform layer and chromatography of the residue was previously described yielded 0.35 g (0.8 mmol, 1%) of the exo isomer **33c** and 3.88 g (9.0 mmol, 10.5%) of the endo isomer **34c**.

Exo isomer 33c was an oil: nmr δ 8.87 (s, 2 H), 7.92 (d, 2 H), 7.20 (d, 2 H), 5.92–4.67 (6 H), 2.93 (t, 2 H), 2.33 (s, 3 H), 1.33 (t, 3 H), 1.23 (t, 3 H); uv λ_{max} 256, 231 nm.

Endo isomer 34c had mp 147–150° from 2-propanol; nmr δ 8.87 (d, 1 H, 3 Hz), 8.57 (d, 1 H, 3 Hz), 7.82 (d, 2 H), 7.13 (d, 2 H), 3.87–4.47 (6 H), 2.97 (t, 2 H), 2.35 (s, 3 H), 1.33 (t, 3 H), 1.22 (t, 3 H); ir ($CHCl_3$) 5.80, 6.10, 6.45 μv; uv λ_{man} 315, 273, 225 nm.

Anal. Calcd for $C_{19}H_{23}N_3O_6S$: C, 54.1; H, 5.5; N, 10.0. Found: C, 54.0; H, 5.5; N, 9.8.

1-Methyl-2-*p*-toluenesulfonamido-5-ethoxycarbonyl-1,4,5,6-tetrahydropyrimidine (37).—To 10.4 g (31 mmol) of **36a** dissolved in 150 ml of glacial acetic acid were added 3.0 ml of 12 *N* hydrochloric acid and 0.7 g of platinum oxide. The mixture was shaken at 50 psi for 3 hr, at which time hydrogen uptake had ceased. Filtration, evaporation, and re-solution in chloroform was followed by washing twice with saturated sodium bicarbonate, drying, and evaporating. The residue was recrystallized from benzene–hexane to give 9.8 g (29 mmol, 93%) of tetrahydropyrimidine **37**: mp 114–116; nmr δ 7.70 (d, 2 H), 7.15 (d, 2 H), 4.10 (quartet, 2 H), 3.45 (d, 4 H), 2.98 (s, 3 H), 1.20 (t, 3 H); ir ($CHCl_3$) 5.79, 6.30, 6.40 μ; uv λ_{max} 232 nm (ε 17,100).

Anal. Calcd for $C_{15}H_{21}N_3O_4S$: C, 53.1; H, 6.2; N, 12.4. Found: C, 52.8; H, 6.1; N, 12.3.

The identical procedure was satisfactory for the reduction of all the other 2-tosylamido- and 2-tosylimidopyrimidines.

2-(*N*-methyl-*p*-toluenesulfonamido)-5-ethoxycarbonyl-1,4,5,6-tetrahydropyrimidine (35) (yield 76%) was a colorless oil: nmr δ 8.25 (s, 1 H), 7.58 (d, 2 H), 7.23 (d, 2 H), 4.10 (q, 2 H), 3.43–3.63 (m, 4 H), 3.00 (s, 3 H), 2.50–2.82 (m, 1 H), 2.37 (s, 3 H), 1.22 (t, 3 H); ir ($CHCl_3$) 5.80, 6.06 μ; uv λ_{max} 228 nm (ε 16,400).

1-Ethoxycarbonylmethyl-2-*p*-toluenesulfonamido-5-ethoxycarbonyl-1,4,5,6-tetrahydropyrimidine (38) (yield 86%) was crystallized from benzene–hexane: mp 108–110°; nmr δ 7.70 (s, 1 H), 7.62 (d, 2 H), 7.10 (d, 2 H), 4.12 (q, 2 H), 4.07 (s, 2 H), 4.00 (q, 2 H), 3.53 (d, 4 H), 2.97 (quintet, 1 H), 2.33 (s, 3 H), 1.57 (t, 3 H), 1.52 (t, 3 H); ir ($CHCl_3$) 5.74, 6.25, 6.45 μ; uv λ_{max} 230 nm.

Anal. Calcd for $C_{18}H_{25}N_3O_6S$: C, 52.6; H, 6.1; N, 10.2. Found: C, 52.6; H, 6.1; N, 10.3.

1-(2-Ethoxycarbonylethyl)-2-*p*-toluenesulfonamido-5-ethoxycarbonyl-1,4,5,6-tetrahydropyrimidine (40) (yield 91%) was crystallized from benzene–hexane: mp 93–95°; nmr δ 7.73 (d, 2 H), 7.20 (d, 2 H), 4.08, 4.05 (overlapping doublets, 4 H), 3.63, 3.57 (overlapping triplet and doublet, 6 H), 2.97 (quintet, 1 H), 2.53 (t, 2 H), 2.37 (s, 3 H), 1.22, 1.18 (overlapping triplets, 6 H); ir ($CHCl_3$) 5.80, 6.30, 6.46 μ; uv λ_{max} 232 nm.

Anal. Calcd for $C_{19}H_{27}N_3O_6S$: C, 53.6; H, 6.4; N, 9.9. Found: C, 53.7; H, 6.2; N, 10.2.

1-Ethoxycarbonylmethyl-2-*p*-toluenesulfonimido-3-methyl-5-ethoxycarbonylhexahydropyrimidine (39). Method A.—A hot solution of **38** (4.98 g, 12.1 mmol) in 100 ml of absolute ethanol was added to 30 ml of 0.42 *N* sodium ethoxide–ethanol. The resulting solution was evaporated to dryness, the residue was dissolved in DMSO, excess methyl iodide was added, and the reaction mixture was stirred at room temperature for 10 hr. After the solvent was removed by distillation, the residue was dissolved in chloroform, washed with water, and chromatographed, employing 1% C_2H_5OH–$CHCl_3$ as the eluent. The only two products isolated were recovered starting material **43** (2.26 g, 5.5 mmol, 45%) and the 3-methyl isomer **39** (1.95 g, 4.6 mmol, 38%).

Method B.—To 1.3 g (38 mmol) of **37** dissolved in 55 ml of dry benzene was added 0.18 g of sodium hydride as a 56% oil dispersion. After 15 min, when the evolution of hydrogen had ceased, ethyl bromoacetate (50% excess) was added. After the reaction had been warmed at 60–70° for 12 hr, hydrogen chloride was bubbled through the solution. The mixture was filtered to remove sodium chloride and bromide, and evaporated to dryness. Chromatography of the resulting oil yielded 0.53 g (1.6 mmol, 42%) of starting material **37** and 0.84 g (2.0 mmol, 52%) of the alkylated product **39**, identical with that from method A: mp 152–163°; nmr δ 7.62 (d, 2 H), 7.07 (d, 2 H), 4.12 (q, 2 H), 3.98 (q, 2 H), 3.55 (d, 4 H), 3.17 (s, 3 H), 2.97 (quintet, 1 H), 2.33 (s, 3 H), 1.23, 1.17 (overlapping triplets, 6 H); ir ($CHCl_3$) 5.76, 6.37, 6.61 μ; uv λ_{max} 224 nm.

Anal. Calcd for $C_{19}H_{27}N_3O_6S$: C, 53.6; H, 6.4; N, 9.9. Found: C, 53.6; H, 6.1; N, 9.8.

1-Ethoxycarbonylmethyl-2-(*N*-methyl-*p*-toluenesulfonamido)-5-ethoxycarbonyl-1,4,5,6-tetrahydropyrimidine (36).—To 25 ml of benzene containing 0.39 g (1.1 mmol) of **35** was added 0.06 g (1.5 mmol) of sodium hydride as a 56% oil dispersion. The mixture was heated to reflux and 0.44 g (2.7 mmol) of ethyl bromoacetate was added. After 24 hr the reaction mixture was cooled, flushed with hydrogen chloride, filtered, and evaporated to dryness. Chromatography gave 0.20 g (0.57 mmol, 51%) of recovered starting material **35** and 0.13 g (0.31 mmol, 30%) of the alkylated product **36** as a clear, colorless oil: nmr δ 7.65 (d, 2 H), 7.20 (d, 2 H), 4.17, 4.13 (overlapping quintets, 4 H), 3.54 (d, 4 H), 3.13 (m, 1 H), 2.77 (s, 3 H), 2.38 (s, 3 H), 1.28, 1.26 (overlapping triplets, 6 H); ir ($CHCl_3$) 5.69, 6.09 μ; uv λ_{max} 228 nm.

Anal. Calcd for $C_{19}H_{27}N_3O_6S$: C, 53.6; H, 6.4; N, 9.9. Found: C, 53.6; H, 5.8; N, 9.8.

***N,N'*-Dimethyl-*N*-(2-ethoxycarbonylethyl)thiourea (43).**—Methyl isothiocyanate (1.0 g, 13.7 mmol) was dissolved in 10 ml of ether and cooled to 0°. Ethyl β-*N*-methylaminopropionate (1.80 g, 13.7 mmol) dissolved in 5 ml of ether was then added dropwise over a 15-min period. The reaction mixture was allowed to stir for 1 hr at 0° and then to warm to room temperature over the next 2 hr. Removal of the solvent *in vacuo* gave **43** as a clear oil in 92% yield, 2.58 g: tlc R_f 0.57, eluting with 5% CH_3OH–$CHCl_3$; nmr δ 6.71 (broad d, 1 H, –NH–), 4.13 (q, 2 H), 4.08 (t, 2 H), 3.18 (s, 3 H), 3.06 (d, 3 H), 2.70 (t, 2 H), 1.25 (t, 3 H).

Anal. Calcd for $C_8H_{16}N_2O_2S$: C, 47.0; H, 7.9; N, 13.7; S, 15.7. Found: C 47.1; H, 8.2; N, 13.6; S, 15.9.

***N,N'*-Dimethyl-*N*-(2-ethoxycarbonylethyl)chloroformamidinium Chloride (44).**—A solution of 1.0 g (4.9 mmol) of thiourea **43** dissolved in 8 ml of THF was treated at room temperature with 0.6 g (6.1 mmol) of $COCl_2$ dissolved in 5 ml of THF and the reaction mixture was allowed to stir overnight. Addition of ether precipitated the product as an orange oil: ir showed the reported characteristic C=N absorption at 6.05 μ;[32] nmr ($CDCl_3$–DMSO-d_6) δ 4.17 (t, 2 H), 4.13 (q, 2 H), 3.57 (s, 3 H), 3.32 (s, 3 H), 2.87 (m, 2 H), 1.25 (t, 3 H).

***N,N',N''*-Trimethyl-*N,N'*-di(2-ethoxycarbonylethyl)guanidine Hydrochloride (45).**—Phosgene (1 g) was dissolved in 50 ml of THF at 0° and a solution of *N,N'*-dimethyl-*N*-(2-ethoxycarbonylethyl)thiourea (**43**) (450 mg, 2.20 mmol) was added dropwise over a period of 45 min. The reaction was allowed to warm to room tenperature, where it was maintained for 3 hr. The phosgene was removed with a stream of dry N_2 (3 hr), the remaining THF was removed *in vacuo*, the residue was dissolved in 25 ml of THF, and the solvent was evaporated again. The residual oil was dissolved in 20 ml of acetonitrile and a solution of ethyl β-*N*-methylpropionate (576 mg, 4.40 mmol) in 10 ml of acetonitrile was added dropwise at 0°, where the solution was kept for 1 hr and then allowed to stir at room temperature overnight.

The acetonitrile was removed *in vacuo* and the residue was dissolved in 25 ml of water and applied to a 400-ml column of Bio-Rad AG 50W-X4 (50–100 mesh) ion-exchange resin. The column was eluted with 4.2 l. of 0.2 *N* HCl to remove ethyl β-*N*-methylpropionate hydrochloride and then with 3.6 l. of 4 *N* HCl to remove the product guanidine hydrochloride as its diacid. The water was removed *in vacuo*, the residue was dissolved in 100 ml of 2-propanol, and the 2-propanol was evaporated to a residue which was dissolved in 50 ml of ethanol and the solution was saturated with HCl at 0°, then stirred for 3 hr, during which the temperatue rose to 20°. Removal of the ethanol and application of the residue to a silica column eluting with 20% CH_3OH–$CHCl_3$ followed by evaporation left the pentasubstituted guanidine hydrochloride **45** as a colorless oil (386 mg, 52% yield): nmr (CD_3OD) δ 4.15 (q, 4 H), 3.60 (m, 4 H), 3.00 (s, 6 H), 2.92 (s, 3 H), 2.77 (t, 4 H), 1.25 (t, 6 H); mass spectrum *m/e* 301 (M^+), 256 ($M^+ - OCH_2CH_3$).

Procedure for the Cyclization to the Imidazolinones. $\Delta^{1,5a}$-2-Oxoimidazolino[1,2-*a*]-8-methyl-6-ethoxycarbonylhexahydropyrimidine (50).—To 1.4 g (3.3 mmol) of **39** in a Kel-F reaction vessel[11] was added 5 ml of anhydrous HF. The vessel was sealed and stirred at room temperature for 2 hr, the HF was removed, the residue was partitioned between water and CH_2Cl_2, and the CH_2Cl_2 was evaporated to give 0.53 g (90%) of *p*-toluenesulfonyl fluoride. The aqoeous phase was adjusted to pH 9 with 5% potassium carbonate and lyophilized, the residue was digested with 1:1 C_2H_5OH–$CHCl_3$ and filtered, and the filtrate was evaporated to dryness. Chromatography of the residue on neutral alumina, activity III, employing 1:1 C_2H_5OH–$CHCl_3$ as the eluent and crystallization from benzene–hexane gave 0.67 g (3.0 mmol, 90%) of pure imidazolinone **50**: mp 121–123°; nmr δ 4.20 (q, 2, H), 3.93 (s, 2 H), 3.62 (d, 4 H), 3.17 (quintet,

1 H), 3.17 (s, 3 H), 1.27 (t, 3 H); ir ($CHCl_3$) 5.80, 5.90, 6.26 μ; uv (pH 12) λ_{max} 223 nm (ϵ 19,800).

Anal. Calcd for $C_{10}H_{15}N_3O_3$: C, 53.3; H, 6.7; N, 18.7. Found: C, 53.1; H, 6.8; N, 18.8.

The identical procedure was satisfactory for the synthesis of the other imidazolinones. The monocyclic imidazolinones were converted to hydrogen chloride salts for characterization by passing hydrogen chloride through a THF solution of the imidazolinone.

1-Methyl-2-(*N*-methyl-*N*-ethoxycarbonylmethyl)aminoimidazolin-4-one (46a) (yield 88%) was crystallized from 2-propanol–ether: mp 171–172°; nmr (D_2O) δ 4.60 (s, 4 H), 0.00 (q, 2 H), 3.35 (s, 6 H), 1.30 (t, 3 H); uv (pH 12) λ_{max} 229 nm (ϵ 21,500).

Anal. Calcd for $C_9H_{16}N_3O_3Cl$: C, 43.3; H, 6.5; N, 16.8. Found: C, 43.0; H, 6.4; N, 17.0.

1-Methyl-2-(*N*-methyl-*N*-carboxymethyl)aminomidazolin-4-one (46b) (yield 19%) had nmr (D_2O) δ 4.38 (s, 4 H), 3.32 (s, 6 H); uv (pH 12) λ_{max} 229 nm (ϵ 22,000).

46b HCl had mp 197–199° dec; nmr (D_2O) δ 4.33 (s, 2 H), 3.25 (s, 9 H); uv (pH 12) λ_{max} 227 nm (ϵ 17,600).

Anal. Calcd for $C_7H_{12}N_3O_3Cl$: C, 40.6; H, 6.8; N, 23.7. Found: C, 40.6; H, 6.8; N, 23.7.

1-Methylimidazolin-2-oxo[1,2-*a*]-$\Delta^{8,8a}$-6-ethoxycarbonyltetrahydropyrimidine (48) (yield 45%) was an oil: nmr δ (4.05 (q, 2 H), 3.74 (s, 2 H), 3.55 (2 H), 2.88 (s, 3 H), 2.86 (m, 1 H), 1.16 (t, 3 H); ir ($CHCl_3$) 5.76, 6.02 μ; uv (0.01 *N* NaOH–absolute EtOH) λ_{max} 210 nm (ϵ 9750); mass spectrum *m/e* 225 (M^+).

$\Delta^{1,9a}$-Tetrahydropyrimidin-2-oxo[1,2-*a*]-7-ethoxycarbonylhexahydropyrimidine (51) (yield 33% from benzene–hexane) had mp 227–230; nmr δ 4.10 (q, 2 H), 3.40 (d, 4 H), 3.33 (t, 2 H), 3.0 (m, 1 H), 2.45 (t, 2 H), 1.17 (t, 3 H); ir ($CHCl_3$) 5.79, 6.20 μ; uv (0.01 *N* NaOH–absolute EtOH) λ_{max} 227 nm (ϵ 21,500).

Anal. Calcd for $C_{10}H_{15}N_3O_3$: C, 53.3; H, 6.7; N, 18.7. Found: C, 53.1; H, 6.5; N, 18.5.

$\Delta^{1,8a}$-2-Oxoimidazolino[1,2-*a*]-6-ethoxycarbonylhexahydropyrimidine (49) (yield 32% from benzene–hexane) had mp 202–204°; nmr (DMSO-d_6) δ 8.35 (s, 1 H), 4.10 (q, 2 H), 3.67 (s, 2 H), 3.42 (d, 4 H), 3.12 (quintet, 1 H), 1.18 (t, 3 H); ir (KBr) 5.82, 6.10, 6.39 μ; uv (0.01 NaOH–absolute EtOH) λ_{max} 229 nm (ϵ 16,400).

Anal. Calcd for $C_9H_{13}N_3O_3$: C, 51.2; H, 6.2; N, 19.9. Found: C, 51.0; H, 6.2; N, 20.0.

Deuterium Exchange.—For each of the deuterium-exchange reactions, 20–30 mg of sample was dissolved in *ca.* 0.5 ml of a deuterated phosphate buffer of the desired pD. The phosphate buffers were prepared by dissolving phosphorus pentoxide in deuterium oxide and adjusting the pD with a previously prepared sodium deuteroxide solution. The three buffers utilized were of pD's 3, 7, and 10 ($\pm$0.5). The amount of exchange was determined from the nmr spectra, taken at intervals. This was determined by measuring the total integral of the ethyl ester methylene, the imidazolinone methylene, and the –OH spinning side band which coincided with the absorptions of interest. Subtracting the –OH spinning side band, determined by integrating the spinning side band downfield from the –OH peak, and the ethyl methylene, which was equal to two-thirds of the ethyl ester methyl integral, from the total integral gave the value of the integral of the imidazolinone signal. This divided by two-thirds of the ester methyl integral which was widely separated from other absorptions and easily integrated, give the per cent protium remaining. The difference was the amount of exchange.

Registry No.—**3**, 2651-15-2; **4a**, 16817-16-6; **4b**, 38653-55-3; **5a**, 38653-56-4; **5b**, 38653-57-5; **5c**, 38653-58-6; **6** (x = 1; R = Et), 38653-59-7; **8a**, 38653-60-0; **8b**, 38653-61-1; **9**, 2973-83-3; **10a**, 20979-72-0; **10b**, 38653-64-4; **11a**, 27703-15-7; **11b**, 38653-66-6; **12a**, 38653-67-7; **12b**, 38653-68-8; **12c**, 38653-69-9; **14**, 1424-52-8; **15**, 38653-71-3; **16**, 38653-72-4; **17a**, 38653-73-5; **17b**, 38653-74-6; **18**, 108-52-1; **19**, 38653-76-8; **20a**, 38652-87-8; **20b**, 38652-88-9; **21a**, 38652-89-0; **21b**, 38652-90-3; **22a**, 38652-91-4; **22b**, 28858-47-1; **23**, 38652-93-6; **24**, 38652-94-7; **25**, 38652-95-8; **26a**, 38652-96-9; **26b**, 38652-97-0; **27**, 6584-12-9; **28**, 87-13-8; **29**, 38653-00-8; **30**, 38653-01-9; **31**, 38653-02-0; **32**, 38653-03-1; **33a**, 38653-04-2; **33b**, 38653-05-3; **33c**, 38653-06-4; **34a**, 38653-07-5; **34b**, 38653-08-6; **34c**, 38653-09-7; **35**, 38653-10-0; **36**, 38653-11-1; **37**, 38653-12-2; **38**, 38653-13-3; **39**, 38653-14-4; **40**, 38653-15-5; **43**, 38653-16-6; **45**, 38653-17-7; **46a**, 38653-18-8; **46b**, 38653-19-9; **46b** HCl, 38653-20-2; **48**, 38653-21-3; **49**, 38653-22-4; **50**, 38653-23-5; **51**, 38653-24-6; β-alanine, 107-95-9; ethyl 3-*N*-methylaminopropionate, 2213-08-3; sarcosine ethyl ester, 13200-60-7; *p*-toluenesulfonyl chloride, 98-59-9; phosgene, 75-44-5; *p*-toluenesulfonyl fluoride, 455-16-3.