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MODELS OF FOLATE COENZYMES—VII[1]

SYNTHESIS AND CARBON TRANSFER REACTIONS OF N^5,N^{10}-METHENYL AND N^5,N^{10}-METHYLENETETRAHYDROFOLATE MODELS

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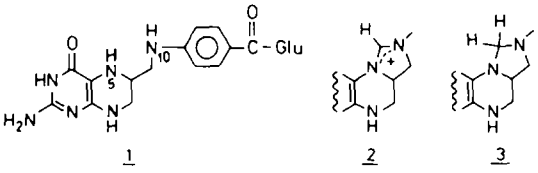
Abstract—Carboxylate esters react with 1,2-diaminoethanes to yield imidazolines, which upon consecutive reaction with acetic anhydride or tosyl chloride and methyl iodide give imidazolinium salts that serve as models of N^5,N^{10}-(CH^+)-tetrahydrofolate (THF) coenzymes (**7a**, **b** and **18a**, **b**). Reduction of the latter salts with sodium borohydride or reaction with anions (R^-) give the corresponding 5,10-[CH(H, R)]-THF models. Mono- and bifunctional nucleophiles react with **18a**, **b** to yield carbon-transfer products. 6-Alkylamino-1,3-dimethyluracils react with 1-tosyl-3,4,4-trimethylimidazolidine (the reduction product of **18b**), in the presence of acetic acid, to form carbon-transfer products via a mechanism which bears close analogy to the mechanism of action of thymidylate synthetase.

Tetrahydrofolate coenzymes are involved in the biochemical transfer of a one-carbon fragment at different oxidation levels.[3] Six one-carbon derivatives of tetrahydrofolic acid (THF **1**) are known and their role in the enzyme-catalyzed transfer of a C_1-unit at the level of formate, formaldehyde and methanol has been recognized. The mechanisms of action of the various coenzymes has received a great deal of attention in recent years.[4a,b] In contrast, only a few scattered attempts have been made to mimic the carbon-transfer process in model reactions.[5a-g] The development of suitable coenzyme models for potential utilization in the "biomimetic transfer" of C_1-units and larger (eventually functionalized) carbon-fragments is an intriguing challenge. In recognition of this a programme directed to the synthesis and application of such models has been initiated in this laboratory and preliminary results have been reported.[6a-d] In this paper we present the details of our study on the models of N^5,N^{10}-methyl- and N^5,N^{10}-methylene-tetrahydrofolate coenzymes **2** [5, 10-(CH^+)-THF] and **3** [5,10-$-CH_2$)-THF] (partial structures), respectively.



1 2 3

A salient feature of the *chemically active* diaminoethane moiety of tetrahydrofolate is the difference in basicity of the two amino functions. The pK_a values of N(5) and N(10) are evaluated as 4.8–5.5 and −1.3,[7a,b] respectively. The facility of reaction and the regioselectivity of ring opening of 5,10-(CH_2)-THF (**4**) is directly influenced by the difference in basicities of the two nitrogens.[8a,b,9] It is obvious from the foregoing comments that an accurate model of **3** would require a significant variation in the basicities of the nitrogens [N-1 and N-3 in the imidazolidine moiety] as an essential structural element.

Synthesis of 5,10-(CH^+)-THF and 5,10-(CH_2)-THF models

The simplest models of **2** and **3** would be imidazolinium salts and imidazolidines, respectively. Imidazoline (**4a**) itself is described in the literature.[10] However, it is not simple to prepare and convenient to handle, due to its reactivity with carbon dioxide under atmospheric conditions. Consequently, for our initial experiments, we chose 2-phenylimidazoline (**4b**)[11] as a stabilized imidazoline species. N-3 of **4b** was acetylated or tosylated and the resulting products (**5a**,**b**) methylated with methyl iodide to yield the salts (**6a**,**b**). Exchange of iodide in the latter salts, by perchlorate ion gave the crystalline perchlorates **7a**,**b**. The compounds **6a**,**b** and **7a**,**b** may be regarded as 2-phenylsubstituted models of the coenzyme 5,10-(CH^+)-THF (**2**). Their assigned structures followed from the relevant spectral data (see Experimental Section). In order to convert models **7a**,**b** to the corresponding 5,10-(CH_2)-THF systems, the reduction of salts (**7a**,**b**) was investigated. Treatment of **7a** and **7b** with $NaBH_4$ exhibited significant differences. Under identical conditions (excess $NaBH_4$/EtOH), while reduction of **7a** yielded the expected imidazolidine **8**—which could be hydrolyzed to benzaldehyde (**9**)—the tosyl derivative **7b**, on the other hand, gave N-benzyl, N-methyl, N′-tosyl-1,2-diaminoethane (**10b**) (Scheme A). The formation of **10b** is rationalized on the basis of an initial reduction step, leading to imidazolidine **11**, followed by ring-opening of the latter, presumably via a boron complex intermediate (**12**), which is further reduced by the borohydride reagent. Some support for this pathway to the "over-reduction" product is derived from the reaction of **7a** with 3,5-diethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine (Hantzsch ester). Although the Hantzsch ester is known to reduce iminium salts to amines,[12] when **7a** is allowed to react with one equivalent of this reagent, a mixture of the diamino derivatives **10a** and the starting material (as the hydrolyzed product, following work-up) was obtained. Use of two equivalents of the Hantzsch ester led to the formation of **10a** in good yield. That intermediates of the types **8** and **13**, by analogy to **11** and **12**, are involved, is concluded from the observation that whereas **8** (prepared by $NaBH_4$ reduc-

tion of **7a**) did not react with Hantzsch ester, addition of an equivalent amount of the *protonated* 3,5-diethoxycarbonyl-2,6-dimethylpyridine—the oxidation product of Hantzsch ester—caused a rapid conversion of **8** to **10a**. The presence of the added "acid" is obligatory for ring-opening of **8** to the iminium intermediate **13**. The difference in the behaviour of **7a** and **7b** upon sodium borohydride reduction can be explained by assuming that the boron reagent complexes more readily with the sulfonamide group than with the acetamide moiety.[13]

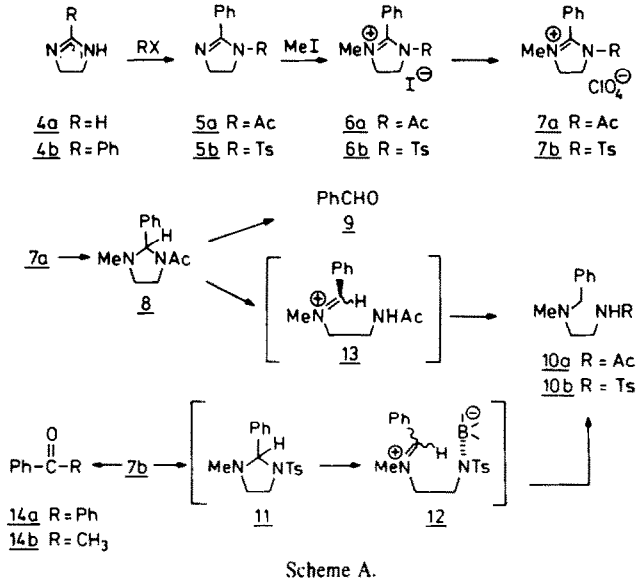
To examine the utility of the imidazolinium derivative **7b** as a carbon-transfer reagent, the salt was allowed to react with carbon nucleophiles (Grignard reagents: PhMgCl, CH_3MgI). Hydrolysis of the primary products led to the formation of benzophenone (**14b**) and acetophenone (**14b**), respectively.

Encouraged by the results on the chemistry of **7a,b**, we turned our attention to the synthesis of the imidazolinium salts as models of 5,10-(CH^+)-THF. Since, as it has been already mentioned, imidazoline itself is unstable, we considered the possibility of stabilizing the heterocyclic ring system by the incorporating gem-dialkyl substituents at the 4- and 5-positions. While reaction of 1,2-diamines with esters is not the preferred route to imidazolines and new, more effective, methods have been recently reported;[14a,b] the reaction of diamines **15a,b** with ethyl formate provided the corresponding substituted imidazolines **16a,b**, in good yields. Conversion to the desired 5,10-(CH^+)-THF models (**18a,b,c**) was carried out by acetylation or tosylation (of the imidazolines) and subsequent methylation (Scheme B, sequence **16a,b→17a,b,c→18a,b,c**). The last mentioned salts were crystalline compounds which could be conveniently used for further studies.

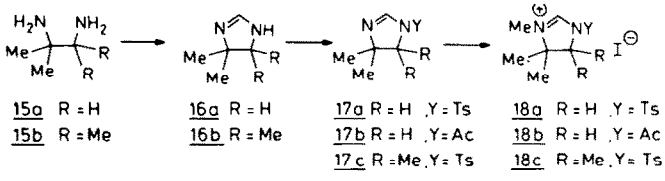
Carbon transfer via 5,10-(CH^+)-THF and 5,10-(CH_2)-THF models

In biological reactions mediated by coenzymes **2** and **3** the central carbon (between N^5 and N^{10}) is transferred to carbon and nitrogen nucleophiles (e.g. serine transhydroxymethylase, thydimylate synthetase and the transformylases). In order to examine the potential of models **18a–c** for an analogous transfer, the salts were allowed to react with several types of nucleophiles. It was recognized that a comparison of the behaviour of **18a,b** with that of **18c** would reveal the role of the extra methyl groups in the model.

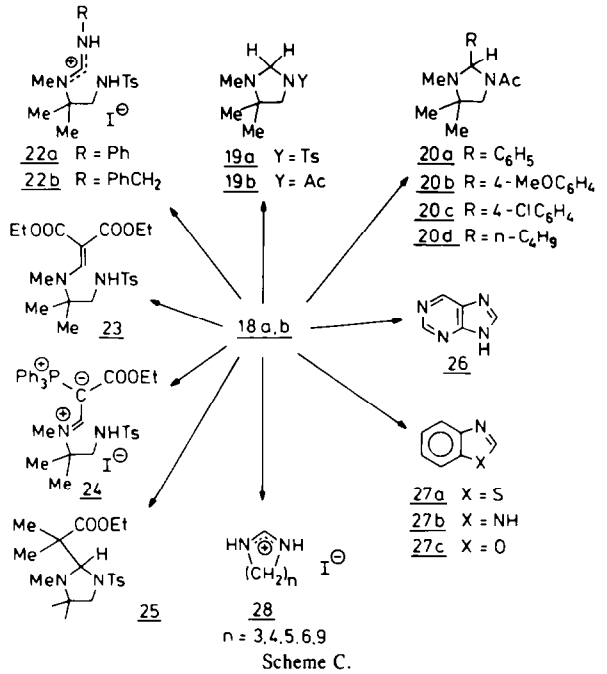
The results of the reactions of **18a,b** with diverse mono- and bifunctional nucleophiles are presented in Scheme C. Sodium borohydride reduction of **18a,b**, under controlled conditions (vide experimental) lead to the imidazolidine derivatives **19a,b**, respectively in excellent yields. The latter compounds are, in fact, 5,10-(CH_2)-THF models, whose carbon-unit transfer reactions are described in the sequel. Reactions of **18b** with Grignard reagents (4-XC_6H_4MgBr, X=H, MeO, Cl) gave imidazolidines **20a–c**, which could be hydrolyzed to the corresponding aldehydes (**21a–c**). The overall process, which proceded in yields ranging from 45–90%, represents a formyl transfer to carbon nucleophiles. An aliphatic Grignard reagent (nBuMgBr) reacted with **18b** to form **20d** (in low yield 28%), whose hydrolysis to the corresponding aldehyde did not proceed satisfactorily. Attempts to achieve an analogous formyl transfer to nitrogen nucleophiles (reactions of **18a** with $C_6H_5NH_2$, $C_6H_5CH_2NH_2$) led to attack on the central carbon, followed by ring-opening of the resulting imidazolidines to give the more stable amidinium salts (**22a,b**). A similar pattern of reactivity, involving nucleophilic attack and



Scheme A.



Scheme B.

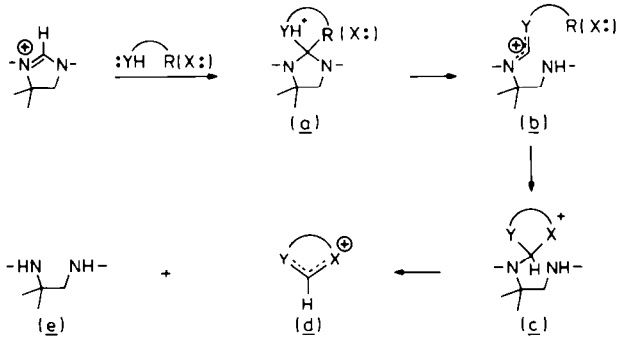


Scheme C.

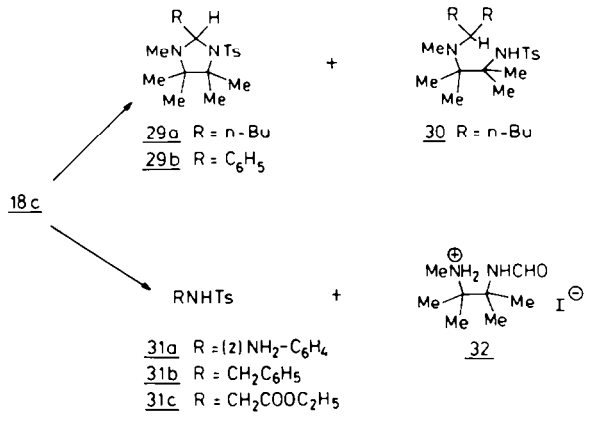
subsequent ring-opening, was also observed for reactions of **18a** with malonate ion (product = **23**) and with the ylid $Ph_3P^+CH^-COOEt$ (product = **24**. That this behavior is linked to the availability of an acidic proton in the primary imidazolidine adduct **a** (Y=–NH, HCCOOEt: Scheme D), is attested by the fact that the anion of ethyl 2-methylpropionate added to **18a** to give the substituted imidazolidine **25** as a crystalline product, m.p. 83–85°. The products **22–24** correspond to **b** in the Scheme D.

The mechanistic sequence sketched in Scheme D suggests a further synthetically useful transformation of species **b**. If the original nucleophile HŸ–R carries a second nucleophilic centre X: (in place of group R), then an intramolecular reaction between the electrophilic and the nucleophilic centres in **b** would result in the formation of **c**. Fragmentation of the latter intermediate involving loss of the diamino moiety (**e**) should lead to heterocycle **d**, incorporating the carbon unit transferred from the coenzyme model. Examples of such carbon transfer to bifunctional nucleophiles are represented by the reactions of **18a** with: (i) 4,5-diaminopyrimidine, (ii) 2-aminobenzenethiol, (iii), 1,2-diaminobenzene, (iv) 2-aminophenol and (v) α,ω-diaminoalkanes, which led to **26**, **27a–c** and **28**, respectively (Scheme C). The product **27c** is presumably hydrolyzed under the conditions of the work-up, since the actual compound isolated after the reaction was 2-formamidophenol.

Reactions of nucleophiles with tetramethylimidazolinium salt **18c** are presented in Scheme E. With n-buthylithium a mixture of the expected imidazolidine **29a** and a product **30**, representing attack by 2 equiv of the nucleophile, was obtained. Reaction of **18c** with PhMgBr gave **29b** in 24% yield. The formation of **30** is reminiscent of the reduction of **7b**, and probably arises from an analogous sequence of transformations (Scheme A). The influence of the four methyl substituents (in **18c**) is reflected in two aspects of the reactivity of the system. Firstly, steric hindrance at the reactive centre expresses itself in the low yield of the adduct **29b** (24%). Secondly, the imidazolidine **29b** does not hydrolyse under the same conditions as **20a** or the adduct prepared by the reaction **18a** with PhMgBr. This can again be due to either steric hindrance or to the ring-stabilization effect of the tetraalkyl substitution. The operation of the last mentioned effect is, however, not consistent with the ease of ring-opening leading to **30**. The course of the reaction of **18c** with nitrogen nucleophiles (o-phenylenediamine, benzylamine and ethylglycinate) is clearly indicative of a thwarting hindrance of the methyl groups to attack on the ring atom. Instead of reaction at C-2, the peripheral sulfonyl group becomes the target of reaction with the nucleophile and the products are **31a**, **31b** and **31c**, res-



Scheme D.



Scheme E.

pectively. The displaced amine moiety from this reaction is isolated as the hydrolytic product **32**.

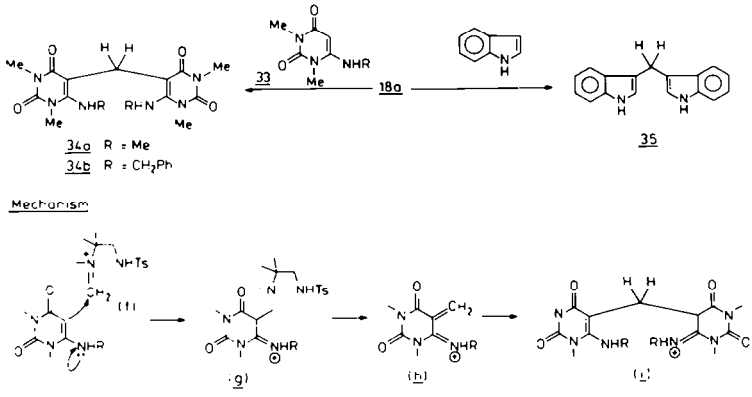
An interesting example of carbon transfer from 5,10-(CH_2)-THF is the thymidylate synthetase catalyzed reaction—conversion of 2'-deoxyuridylate (dUMP) to thymidylate (dTMP)—in which the coenzyme functions as both, a methylene donor and a reducing agent.[15a,b] The mechanism of this reaction has stimulated intensive interest and the current proposal[16] for this (mechanism) involves the following events at the active site. A thiol residue (Cys-198) of the apoenzyme attacks the C-6 of dUMP (substrate) and the resulting nucleophilic centre, generated at C-5, reacts with the iminium moiety $\left(CH_2{=}N^{+}\right)$ formed by acid catalyzed ring-opening of the coenzyme (**3**). Subsequently, the enzyme-coenzyme-substrate complex fragments into an exocyclic methylene intermediate and tetrahydrofolate (THF), via a mechanism, the details of which are as yet not fully established. In a final step, the exocyclic methylene intermediate is reduced by THF, to give dTMP and 7,8-dihydro-THF.

While model studies [5b–d] have shown that an exocyclic methylene intermediate is generated and subsequently reduced to thymine; in the light of the more recent information on the mechanism of action of thymidylate synthetase and in view of the (harsh) reaction conditions (high temperatures) employed in the experiments with "Friedkin intermediate[17] models", it would appear that an examination of systems which approximate the enzyme-coenzyme-substrate complex more closely, are warranted. With this objective we have studied the reaction of 5,10-(CH_2)-THF model **19a** with 1,3-dimethyl-6-aminouracil derivatives **33** (R=Me, $PhCH_2$) in the presence of acetic acid (Scheme F). The products of this reaction at room temperature or lower (0°), are **34a,b** which represent a methylene transfer from the model to two molecules of the substrate. It should be emphasized that in **33**, the electron relay from the C-6 amino substituent generates a nucleophilic centre at C-5 and thereby makes the system correspond to the enzyme-substrate covalent complex. The latter, then reacts with the iminium cation **f**[18] (Scheme F), to form species **g**. The latter is a model of the proposed enzyme-substrate-coenzyme complex. Fragmentation of **g**, presumably gives the exocyclic methylene intermediate **h**, which is quenched by a second molecule of the substrate to yield (**i**), that subsequently tautomerizes to **34(a,b)**. Although detailed information on the individual steps is lacking, the sequence **f→g→h→i**, in the transformation of **33→34**, closely follows the molecular events in the active site of thymidylate synthetase. Reaction of **18a** with indole gives in an analogous reaction the product bis-3-indolylmethane (**35**).

The principle and the ease of carbon transfer via folate coenzyme models makes it a potentially versatile process for synthetically useful transfer of methylene and substituted-methylene fragments. Application of these shall be described in the forthcoming communications. A study of the detailed mechanism of thymidylate synthetase, via model reactions, is also a subject of active interest in our laboratory.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were recorded on an Unicam SP 200 or Perkin-Elmer 257 spectrometer. The absorptions are given in cm^{-1}. PMR spectra were run on Varian



Scheme F.

Associates Model A-60 D and HA-100 instruments. The chemical shifts (δ) are given in ppm using TMS as an internal standard. For the resonance signals the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Spin–spin coupling constants (J) are given in Hertz. Mass spectra were obtained with a Varian Mat-711 spectrometer. Analyses were carried out at the Microanalytical Laboratory, Department of Physical-Organic and Analytical Chemistry, Organic Chemistry Institute, T.N.O. Zeist, The Netherlands.

1-Acetyl-2-phenyl-Δ^2-imidazoline (**5a**)

2-Phenyl-Δ^2-imidazoline (**4b** 426 mg; 3 mmol) was dissolved in 5 ml dry CH_2Cl_2. 375 mg (3 mmol) acetic anhydride and 303 mg (3 mmol) triethylamine dissolved in CH_2Cl_2 were added to the above mentioned mixture, after which the resulting solution was stirred for 45 min at room temp. The mixture was washed with water and dried over Na_2SO_4. After evaporation of the solvent the crude product was purified by chromatography using Al_2O_3 and CH_2Cl_2 ethylacetate 1:19 as eluent. Yield: 334 mg oil (61%). IR ($CHCl_3$): 1660 (s), 1630 (s), 1600 (m), 1580 (w). PMR (CCl_4): 1.68 (s, 3H, $COCH_3$), 3.85 (m, 4H, C^4H_2 and C^5H_2), 7.38 (m, 5H, ArH).

1-Tosyl-2-phenyl-Δ^2-imidazoline (**5b**)

2-Phenylimidazoline (**4b**, 1.4 g, 10 mmol) and 1.1 g of triethylamine were dissolved in 15 ml of dry CH_2Cl_2. After adding 2.1 g tosylchloride the resulting mixture was stirred for 2 hr at room temp. The precipitate was filtered off and the filtrate was washed with dilute sodium bicarbonate sodium and dried over Na_2So_4. Evaporation yielded a thick oil (3 g) which partly solidified upon standing in the refrigerator. After adding diethyl ether with a trace of ethanol, white crystals were obtained which were filtered off. Yield: 3 g (100%); m.p. 87–90°. IR (KBr): 1620 (m), 1595 (m), 1355 (s), 1175 (s). PMR ($CDCl_3$): 2.40 (s, 3H, $ArCH_3$), 3.40–4.20 (m, 4H, C^4H_2 and C^5H_2), 7.10–7.90 (m, 9H, ArH).

1-Acetyl-2-phenyl-3-methyl-Δ^2-imidazolinium Iodide (**6a**)

128 Milligrams (0.68 mmol) of **5a** was dissolved in 5 ml dry CH_2Cl_2. 0.5 ml methyl iodide was added after which the mixture was refluxed for 1 hr. After 1 hr another 0.5 ml portion of methyl iodide was added and the mixture was refluxed overnight. Evaporation yielded 225 mg of **6a** as a yellow foam. IR ($CHCl_3$): 1720 (s), 1640 (s), 1600 (m).

1-Acetyl-2-phenyl-3-methyl-Δ^2-imidazolinium Perchlorate (**7a**)

The salt **6a** (225 mg) was dissolved in 2 ml of dry acetonitrile. To this solution 140 mg (0.68 mmol) $AgClO_4$ was added. The resulting suspension was stirred for 2 hr at room temp. Filtration of the precipitate and evaporation of the solid yield **7a** as yellowish crystals. Yield: 203 mg (92%) m.p. 107–125°. IR (KBr): 1740 (s), 1640 (s), 1600 (w), 1090 (s); PMR ($DMSOd_6$): 1.90 (s, 3H, $COCH_3$), 3.05 (s, 3H, H^3CH_3), 4.30 (m, 4H, C^4H_2 and C^5H_2), 7.70 (s, 5H, ArH).

1-Tosyl-2-phenyl-3-methyl-Δ^2-imidazolinium Iodide (**6b**)

The salt **5b** (3 g) was dissolved in 50 ml of dry CH_2Cl_2. 10 ml of methyl iodide was added and the resulting mixture was refluxed overnight. The next morning another 0.5 ml of methyl iodide was added and the mixture refluxed for another 5 hr. Evaporation of the solvent yielded **6b** as a yellow foam. Yield: 3.9 g (88%). The product was directly converted to the corresponding perchlorate salt (**7b**).

1-Tosyl-2-phenyl-3-methyl-Δ^2-imidazolinium Perchlorate (**7b**)

The salt **6b** (0.88 g) was dissolved in 8 ml of dry acetonitrile. To this soln 414 mg $AgClO_4$ was added and the resulting suspension was stirred for 2 hr at room temp. Filtration of the precipitate and evaporation of the solvent yielded a residue which could be recrystallized from ethanol. Yield: 650 mg crystals (79%); m.p. 174–175°. IR (KBr): 1640 (s), 1595 (m), 1080 (s); PMR (DMSO D_6): 2.38 (s, 3H, $ArCH_3$), 2.87 (s, 3H, N^3CH_3), 3.90–4.60 (m, 4H, C^4H_2 and C^5H_2), 7.20–7.85 (m, 9H, ArH).

Reduction of Perchlorate **7a** *by $NaBH_4$. Formation of* **8**

The perchlorate **7a** (600 mg), dissolved in ethanol (12 ml) was allowed to react with $NaBH_4$ (200 mg) at room temp. After stirring for 2 hr, water was added and the mixture extracted with $CHCl_3$. The cloroform layer was washed with water, dried over Na_2SO_4, filtered and evaporated. Yield of **8**, as an oil, 343 mg (84%). IR ($CHCl_3$): 1630 (–CO–N). PMR (CCl_4): 1.52, 1.92 (2 × s, 2H, $NCOCH_3$, two amide rotamers), 2.21 (s, 3H, NCH_3), 2.30–4.00 (m, 4H, CH_2CH_2), 4.61 and 4.90 (2 × s, 1H, N–CH–N, two rotamers), 7.28 (s, 5H, Ar–H).

Reaction of salt **7a** *with Hantzsch Ester. Formation of* **10a**

The perchlorate **7a** (150 mg, 0.5 mmol) was dissolved in CH_3CN (5 ml) and to this soln 3 equiv Hantzsch ester were added. The mixture was refluxed overnight, the solvent removed by evaporation and the oil washed with ether (5x). The residue was dissolved in $CHCl_3$, the soln. stirred with Na_2CO_3 soln., washed with water, and the organic layer dried and evaporated. The residue was chromatographed on a thick-layer alumina plate (eluents: EtOAc), whereupon besides **10a** (27.5 mg, 27%), the hydrolyzed starting material (26%) was isolated. The imidazolidine **10a** was purified by further thick-layer chromatography. IR ($CHCl_3$): 3405, 1655, 1508. PMR (CCl_4): 1.85 (s, 3H, $COCH_3$), 2.22 (s, 3H, NCH_3), 2.45 (t, 2H, J = 6 Hz, $N–CH_2$), 3.25 (q, after shaking with D_2Ot, 2H, J = 6 Hz, $HN–CH_2$), 3.48 (s, 2H, $ArCH_2$), 6.25 (broad s, 1H, NH), 7.25 (s, 5H, Ar–H).

Reaction of **8** *with a mixture of Hantzsch ester and protonated oxidized Hantzsch ester. Formation of* **10a**

Imidazolidine **8** (104 mg, 0.5 mmol) was dissolved in CH_3CN (3 ml) and to this soln Hantzsch ester (176 mg, 0.7 mmol) and the perchlorate salt of oxidized Hantzsch ester were added (177 mg, 0.5 mmol). The mixture was refluxed overnight, the solvent removed by evaporation and the oil washed with ether (5x). The residue was dissolved in $CHCl_3$, the soln stirred with Na_2CO_3 soln, washed with water, and the organic layer dried and evaporated. The residue was purified by thick-layer chromatography. Yield of **10a** as an oil (48 mg; 50%).

Reduction of Perchlorate **7b** *with $NaBH_4$. Formation of* **10b**

To a soln of **7b** (150 mg, 0.36 mmol) in ethanol (3 ml), $NaBH_4$ (140 mg) was added and the mixture stirred for 2 hr. After addition of water, the mixture was extracted with $CHCl_3$, the organic layer dried and evaporated. The residue was chromatographed on a thick-layer silica gel plate (eluents: $CHCl_3$/EtOAC 1:1), when 85 mg (74%) of **10b** was obtained as an oil. IR ($CHCl_3$): 1600, 1500, 1345, 1150. PMR (CCl_4): 2.02 (s, 3H, NCH_3), 2.20–2.60 (m, 5H, $ArCH_3 + CH_2N$ ), 2.75–3.15 (m, 2H, CH_2NH), 5.18 (broad s, 1H, NH), 7.02–7.35 (m, 7H, Ar–H), 7.70 (d, 2H, J = 8.5 Hz, Ar–H).

Reaction of **7b** *with Grignard Reagents*

The following general procedure was followed. Solutions of Grignard reagents (PhMgBr and MeMgI) in THF were added dropwise to the salt **7b**, suspended in THF. The mixture was treated with water, (in case of MeMgI, with dil. HCl), if necessary filtered, the solvent removed, the residue extracted with $CHCl_3$, and the organic layer washed and dried. The product was chromatographed on a thick-layer silica gel plate. Yield: **14a** (23%); **14b** (13%). It should be emphasized that the experimental procedure has not been optimized.

4,4-Dimethyl-Δ^2-imidazoline (**16a**)

Ethyl formate (14.8 g, 0.2 mmol) was added dropwise to 17.6 g (0.2 mmol) of 1,2-diamino-2-methylpropane, the latter being cooled in ice. After having stirred for 1 hr at room temperature, the reaction mixture was heated and ethanol distilled off. The resulting mixture was heated at 150° for 1 hr. Subsequently, the temperature was raised to 220° and the mixture stirred for 30 min. After cooling, the mixture was distilled under reduced pressure. Yield: 9.4 g (48%); b.p. 80–85°/15 mm. IR ($CHCl_3$): 3450 (m), 3250 broad (m), 1612 (s); PMR ($CDCl_3$): 1.22 (s, 6H, $C^4(CH_3)_2$), 3.25 (s, 2H, C^5H_2), 5.29 (s, 1H, N^1H), 6.92 (s, 1H, C^2H).

4,4,5,5-*Tetramethyl*-Δ^2-*imidazoline* (**16b**)

A mixture of 1,2-diamino-1,2-dimethylbutane (18.5 g, 160 mmol) and ethyl formate (10.7 g, 147 mmol) was refluxed overnight. The excess of the diamine was distilled off after which the remaining residue was distilled under reduced pressure. Yield: 11.4 g yellowish crystals (62%); b.p. 100–120°/10 mm. IR (KBr): 3090 (broad, s), 2960 (s), 1595 (s). PMR ($CDCl_3$): 1.17 (s, 12H, $C^4(CH_3)_2$) and $C^5(CH_3)_2$), 4.80 (s, 1H, N^1H, disappears after equilibration with D_2O), 6.98 (s, 1H, C^2H).

1-*Tosyl*-4,4-*dimethyl*-Δ^2-*imidazoline* (**17a**)

94 g of **16a** (0.96 mol) and 97 g of triethylamine (0.96 mol) were dissolved in 600 ml of dry CH_2Cl_2, cooled in ice, and 182 g (0.96 mol) of tosyl chloride was slowly added in portions. The ice was removed and the mixture was stirred for about an hour in order to allow it to warm to room temperature. The mixture was washed with dilute $NaHCO_3$, water, saturated NaCl and dried over Na_2SO_4. Filtration and evaporation of the solvent yielded **17a** as an oil, which crystallized and was used in the next step without further purification. Yield: 229.7 g (94%); m.p. 75–78°. IR ($CHCl_3$): 2980 (s), 2960 (m), 1615 (s), 1170 (s); IR (KBr): 2965 (s), 2930 (m), 1612 (s), 1355 (s), 1170 (s). PMR ($CDCl_3$): 1.18 (s, 6H, $C^4(CH_3)_2$), 2.47 (s, 3H, $ArCH_3$), 3.21 (s, 2H, C^5H_2), 7.38 (s, 1H, C^2H), 7.42 (d, J = 8 Hz, 2H, C^3H and C^5H Ar), 7.82 (d, J = 8 Hz, 2H, C^2H and C^6H Ar).

1-*Acetyl*-4,4-*dimethyl*-Δ^2-*imidazoline* (**17b**)

Imidazoline **16a** (10 g; 102 mmol) and 10.3 g of triethylamine (120 mmol) were dissolved in 60 ml of dry CH_2Cl_2. After cooling the mixture in ice 10.4 g (102 mmol) of acetic anhydride was slowly added to the mixture. After the addition was complete the ice was removed and the mixture was allowed to warm up to room temp. After 1 hr the mixture was washed with $NaHCO_3$, water, saturated NaCl and dried over Na_2SO_4. Filtration and evaporation of the solvent yielded **17b** as a clear oil which was used in the subsequent step without purification. Yield: 8.9 g oil (62%). IR ($CHCl_3$): 2985 (m), 1675 (s), 1610 (s), 1400 (s). PMR ($CDCl_3$): 1.32 (s, 6H, $C^4(CH_3)_2$), 2.27 (s, 3H, $COCH_3$), 3.50 (s, 2H, C^5H_2), 7.42 (s, 1H, C^2H).

1-*Tosyl*-4,4,5,5-*tetramethyl*-Δ^2-*imidazolidine*(**17c**)

12.6 g of **16b** and 10.1 g of triethylamine were dissolved in 50 ml of dry CH_2Cl_2. The mixture was cooled in ice and over approx. 45 min 17.5 g of tosyl chloride was added in portions. After stirring one night at room temperature the precipitate was filtered off. The organic layer was washed with dilute $NaHCO_3$, three times with saturated NaCl, and dried over $NaSO_4$. Evaporation of the solvent yielded **17c** as yellow crystals. Yield: 24.7 g (88%); m.p. 106–109°. IR (KBr): 1615 (s), 1595 (m), 1345 (s), 1165 (s), 1155 (s). PMR ($CDCl_3$): 1.03 (s, 6H, $C(CH_3)_2$), 1.22 (s, 6H, $C(CH_3)_2$), 2.48 (s, 3H, $ArCH_3$), 7.40 (d, J = 8 Hz, 2H, C^3H and C^5H Ar), 7.48 (s, 1H, C^2H), 7.83 (d, J = 8 Hz, 2H, C^2H and C^6H Ar).

1-*Tosyl*-3,4,4-*trimethyl*-Δ^2-*imidazolinium Iodide* (**18a**)

Imidazoline **17a** (229.7 g) was dissolved in 400 ml of dry CH_2Cl_2. 100 ml of CH_3I were added to the mixture after which it was heated overnight (bath temp. 50°, gentle reflux). After cooling the mixture and filtering off, the product **18a** could be isolated as almost white crystals after washing with cold CH_2Cl_2 (215 g). After concentrating the mother liquor and adding dry ether another 58 g of **18a** could be isolated. Yield: 273 g of crystals (76%); m.p. 166.5–168°. IR (KBr): 1642 (s), 1372 (s), 1192 (s), 1178 (s). PMR ($CDCl_3$): 1.53 (s, 6H, $C^4(CH_3)_2$), 2.42 (s, 3H, $ArCH_3$), 3.55 (s, 3H, N^+CH_3), 3.88 (s, 2H, C^5H_2), 7.49 (d, J = 8 Hz, C^3H and C^5H Ar), 8.22 (d, J = 8 Hz, 2H, C^2H and C^6H and C^6H Ar), 9.34 (s, 1H, C^2H). Found: C, 39.74; H, 4.79; N, 7.08; S, 8.00. Calc for $C_{13}H_{19}N_2O_2SI$: C, 39.59; H, 4.82, N, 7.11; S, 8.12%.

1-*Acetyl*-3,4,4-*Trimethyl*-Δ^2-*imidazolinium Iodide* (**18b**)

Imidazoline **17b** (1.3 g) was dissolved in 6 ml of dry CH_2Cl_2, 3 ml of CH_3I was added to the mixture, which was refluxed for 3 hr. A further 1 ml of MeI was added and the mixture was again refluxed for 3 hr. After cooling the mixture, the precipitate was filtered off and compound **18b** was isolated as white crystals. Yield: 2.2 g of white crystals (80%). M.p. 231–236°. IR (KBr): 2980 (m), 2940 (m), 1730 (s), 1645 (s), 1375 (s), 1285 (s). PMR (D_6-DMSO): 1.48 (s, 6H, $C^4CH_3)_2$), 2.38 (s, 3H, $COCH_3$), 3.30 (s, 3H, N^+CH_3), 3.92 (s, 2H, C^5H_2), 9.45 (s, 1H, C^2H). Found: C, 34.13; H, 5.49; N, 9.89. Calc for $C_8H_{15}N_2OI$: C, 34.00; H, 5.33; N, 9.94%.

1-*Tosyl*-3,4,4,5,5-*pentamethyl*-Δ^2-*imidazolinium Iodide* (**18c**)

Imidazoline **17c** (24.75 g) was dissolved in 100 ml of dry CH_2Cl. After adding 30 ml of MeI the mixture was refluxed for 3 hr, after which another 5 ml of MeI was added and the refluxing continued for 10 hr. The mixture was cooled and the crystalline product which was so formed filtered off. Yield: 33.9 g of white crystals (91%). M.p. 185–187°. IR (KBr): 1638 (s), 1600 (m). PMR (DMSO-D_6): 1.20 (s, 6H, $C(CH_3)_2$), 1.30 (s, 6H, $C(CH_3)_2$), 2.49 (s, 3H, $ArCH_3$), 3.38 (s, 3H, N^+CH_3), 8.12 (d, J = 9 Hz, C^3H and C^5H Ar), 8.65 (d, J = 9 Hz, C^2H and C^6HAr), 9.25 (s,1H, CH).

1-*Tosyl*-3,4,4-*trimethylimidazolidine* (**19a**)

The salt **18a** (1.14 g, 2.9 mmol) was dissolved in 20 ml of dry ethanol. The solution was cooled to 0°C under N_2 and $NaBH_4$ (3.5 mmol) was added and the resulting mixture stirred for 1 hr. To the reaction mixture sat. solution of NH_4Cl and NaCl were added and the organic material extracted with $CHCl_3$, the soln dried over $MgSO_4$ and evaporated. The crude reduction product was purified by chromatography over silica (eluents EtOAc/cyclohexane 1:1). Yield of crystalline **19a**, m.p. 59–60°, 715 mg (92%). PMR (CCl_4): 0.90 (s, 6H, CMe_2), 2.05 (s, 3H, NMe), 2.43 (s, 3H, Ar–Me), 3.04 (s, 2H, ring CH_2–N), 3.96 (s, 2H, N–CH_2–N), 7.30 and 7.73 (d × d, 4H, Ar-protons).

1-*Acetyl*-3,4,4-*trimethylimidazolidine* (**19b**)

The iodide **18b** (540 mg, 2 mmol) was dissolved in ethanol (5 ml) and to the soln cooled in ice $NaBH_4$ (47 mg) was added. After 1 hr, NH_4Cl soln was added and the mixture extracted with $CHCl_3$. The $CHCl_3$ layer was washed, dried and evaporated to yield 285 mg (91%) of the reduced product **19b** as an oil. IR ($CHCl_3$): 1645. PMR ($CDCl_3$): 1.08, 1.10 (2 × s, 6H, 2 × CH_3), 2.01 (s, 3H, CH_3CO), 2.25 (s, 3H, NCH_3), 3.35 (m, 2H, CH_2N), 4.12 (m, 2H, NCH_2N).

1-*Acetyl*-2-*phenyl*-3,4,4-*trimethylimidazolidine* (**20a**)

From 61 mg (2.5 mmol) magnesium and 450 mg (2.9 mmol) of bromobenzene a solution of phenylmagnesium bromide in THF was made in the usual way. The solution was added to a suspension of 540 mg **18b** (1.9 mmol) in 10 ml of freshly distilled THF. The mixture was stirred overnight at room temp. To the resulting soln water was added and the mixture was extracted with ethyl acetate, the organic layer was dried over Na_2SO_4 and evaporation of the solvent yielded a residue which was purified by chromatography (silica, ethyl acetate/dichloromethane 1:1). Yield: 313 mg oil (74%). IR ($CHCl_3$): 2980 (m), 1630 (s); PMR ($CDCl_3$) a mixture of rotational isomers: 1.02 (s, 3H, C^4CH_3), 1.25 (s, 3H, C^4CH_3), 1.62 and 1.98 (2s, total 3H, $COCH_3$), 2.04 (s, 3H, N^3CH_3), 3.36 (d, J = 10.5 Hz), 3.50 (s) and 3.99 (d, J = 10.5 Hz, total 2H, C^5H_2), 4.70 and 4.98 (2s total 1H, C^2H), 7.38 (s, 5H, ArH).

1-*Acetyl*-2-(4-*methoxy phenyl*)-3,4,4-*trimethylimidazolidine* (**20b**)

From 61 mg (2.5 mmol) of magnesium and 525 mg p-bromo anisole (2.8 mmol) a soln of p–MeO phenylmagnesium bromide in THF was made in the usual way. This soln was added to a suspension of 564 mg **18b** (2 mmol) in 7 ml of freshly distilled THF. The mixture was stirred overnight at room temp. To the resulting solution water was added and the mixture was extracted with ethyl acetate, the organic layer washed with saturated NaCl and dried over Na_2SO_4. Evaporation of the solvent yielded a residue which was purified by chromatography (silica, ethyl acetate) and yielded **20b** as a slowly crystallizing oil. Yield: 471 mg (90%); m.p. 86–93°. IR ($CHCl_3$): 2950 (m), 1635 (s), 1625 (s), 1220 (s). PMR ($CDCl_3$): mixture of rotational isomers: 0.97 (s, 3H, C^4CH_3), 1.18 (s, 3H, C^4CH_3), 1.60 and 1.02 (2s, total 3H, $COCH_3$), 2.02 (s, 3H, N^3CH_3), 3.28 (d, J = 10.5 Hz), 3.43 (broad,

s), 3.92 (d, J = 10.5 Hz, total 2H, C^5H_2), 3.75 (broad, s, 3H, $ArOCH_3$), 4.61 and 4.87 (2s, total 1H, C^2H), 6.66–7.45 (m, 4H, ArH).

1-*Acetyl*-2-(4-*Chloro phenyl*)-3,4,4-*trimethylimidazolidine* (**20c**)

From 61 mg (2.5 m mol) magnesium and 530 mg (2.8 mmol) p-chlorobromobenzene a solution of p-chlorophenylmagnesium bromide in THF was made in the usual way. This soln was added to a stirred suspension of 564 mg (2 mmol) of **18b** in 7 ml of freshly distilled THF. The mixture was stirred overnight at room temp. Water was added to the resulting solution and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. Evaporation yielded a residue which was purified by chromatography (silica, ethyl acetate). From the eluate **20c** was isolated as a slowly crystallizing oil. Yield: 500 mg (94%); m.p. 86–91°. IR ($CHCl_3$): 3000 (m), 1640 (s); PMR ($CDCl_3$): a mixture of rotational isomers: 1.02 (broad, s, 3H, C^4CH_3), 1.23 (broad, s, 3H, C^4CH_3), 1.62 and 1.93 (2s total 3H, $COCH_3$), 2.03 (broad, s, 3H, N^3CH_3), 3.30 (d, J = 11 Hz), 3.45 (s) and 3.96 (d, J = 11 Hz, total 2H, C^5H_2), 4.64 and 4.88 (2s, total 1H, C^2H), 7.06–7.62 (m, 4H, ArH).

1-*Acetyl*-2-*n-butyl*-3,4,4-*trimethylimidazolidine* (**20d**)

n-Butylmagnesium bromide was prepared from Mg (1.2 mmol) and n-bromobutane (1.2 mmol) in THF. To this 429 mg of HMPT were added and the reagent added dropwise to salt **18b** (1 mmol) in THF. The mixture was stirred overnight at room temp. and treated with NH_4Cl soln. After adding EtOAc, the organic layer was washed with water, dried and evaporated. The product was chromatographed on a silica gel thick-layer plate (rf. o. 34, eluents: EtOAc), whereupon **20d** was obtained as an oil, yield: 58 mg (28%). IR ($CHCl_3$): 1630. PMR ($CDCl_3$): 0.7–1.00 (m, 6H, ring CH_3, at 0.88 and chain CH_3 as m), 1.00–1.80 (m, 9H, ring CH_3 at 1.07, $+CH_2CH_2CH_2$), 1.86 (s, 3H, $COCH_3$), 2.15 (s, 3H, NCH_3), 2.45, 2.65 [(2 × d, AB pattern J = 7.5 Hz) + 3.07, 3.23 (2 × d, AB pattern J = 9.5 Hz) together 2H, ring-CH_2], 3.70–4.20 (m, 1H, N-CH-N).

Hydrolysis of **20a–c**. *Formation of benzaldehyde, p-methoxybenzaldehyde and p-chlorobenzaldehyde* (**21a–c**)

General procedure. A mixture of the imidazolidine (**20a–c**) (100 mg) and oxalic acid (100 mg) in water was refluxed for 30 min. Extraction with ether, drying over Na_2SO_4 and evaporating, yielded the aldehydes. Yield: **21a** (61%); **21b** (77%); and **21c** (95%). The IR spectra of the aldehydes were identical to those reported in the Sadtler Standard Spectra, Nos 3010, 1946 and 624 respectively.

Reaction of salt **18a** *with aniline and benzyl amine. Formation of* **22a** *and* **22b**

General procedure. A mixture of the amine (1 mmol) and the salt **18a** (1 mmol) in CH_3CN (5 ml) was refluxed overnight. The solvent was evaporated and the residue triturated with ethanol **22a**: m.p. 159–162°. IR (KBr): 3400, 1670, 1330, 1155. PMR ($CDCl_3$): 1.37, 1.42 (2 × s, 6H, 2 × CH_3), 2.31, 2.38 (2 × s, 3H, $ArCH_3$), 2.60–3.20 (m, 2H, CH_2N), 3.30, 3.38 (2 × s, 3H, CH_3-N^+), 6.50–6.90 (m, 1H NHTs), 6.90–8.20 (m, 11H, Ar–H, CH=N+, NHPh). The singlets have different ratios, which points to the presence of two isomers. **22b**: (64%), after recrystallization from ethanol, m.p. 170.5–171.5°. IR (KBr): 3380, 1680, 1330, 1160. PMR (DMSO-d_6): 1.22 (s, 6H, 2 × CH_3), 2.37 (s, 3H, Ar–CH_3), 2.72 (s, 3H, CH_3–N), 2.81 (s, 2H, CH_2N), 3.30 (broad s, 2H, NH), 4.37 (s, 2H, CH_2–Ph), 7.10–7.50 (m, 7H, Ar–H), 7.60–7.80 (m, 3H, two Ar–H + Ch=N+). Found: C, 48.09; H, 5.43; S, 6.54; I, 25.27; N, 8.27. Calc for $C_{20}H_{28}N_3OSI$: C, 47.90; H, 5.52; S, 6.38; I 25.34; N, 8.38%.

1 - *Carbethoxy* - 2 - [2'(4 - *methylbenzenesulphonyl*)*amine* - 1',1' - *dimethyl*]*amino acrylic acid ethyl ester* (**23**)

Sodium hydride (50 mg, 55% suspension in mineral oil 2.1 mmol) was washed with dry benzene and 8 ml of dry freshly distilled THF was added. The mixture was cooled in ice under nitrogen and 320 mg of diethyl malonate (2 mmol) dissolved in 2 ml of THF was added. After the mixture had stirred for 10 min at 0°, 788 mg (2 mmol) of **18a** was added. The mixture was vigorously stirred and allowed to warm to room temperature. After the salt had dissolved the mixture was concentrated under reduced pressure. The residue was filtered over silica gel with ethyl acetate as the eluent. Concentration of the filtrate yielded a residue which was recrystallized from ether. Yield: 700 mg of white crystals (82%); m.p. 105–107°. IR (KBr): 3205 (m), 1680 (m), 1650 (s), 1640 (s), 1375 (m), 1150 (s); PMR ($CDCl_3$): 1.28 (t, J = 7 Hz, 6H, 2 × $COOCH_2\underline{CH_3}$), 1.35 (s, 6H, $C^{11}(CH_3)_2$), 2.42 (s, 3H, $ArCH_3$), 2.67 (s, 3H, NCH_3), 2.97 (d, J = 6.5 Hz, 2H, C^2H_2, 4.2 (q, J = 7 Hz, 4H, 2 × $COO\underline{CH_2}CH_3$), 5.53 (broad t, J = 6.5 Hz, N^3H), 7.30 (d, J = 8.5 Hz, 2H, C^3H and C^5(H)Ar), 7.69 (s, 1H, C^2H), 7.78 (d, J = 8.5 Hz, 2H, C^2H and C^6H Ar).

1 - *Triphenylphosphinidino* - 2 - [2'(4 - *methylbenzenesulphonyl*)-*amino* - 1',1' - *dimethyl*]*aminoacrylic acid methyl ester* (**24**)

The salt **18a** (3.94 g, 10 mmol) and 3.34 g of carbomethoxy triphenylmethylidenephosphorane (10 mmol) were dissolved in 25 ml of dry acetonitrile. After 1 night at room temp. the crystalline reaction product was filtered off. After concentration of the filtrate, another crop of crystals could be collected. Yield: 6.9 g of light yellow crystals (85%); m.p. 196–198°. Product contains a molecule of CH_3CN in its structure. IR (KBr): 3060 (m), 1695 (s), 1590 (s), 1365 (s), 1155 (s); PMR ($CDCl_3$): 1.07 (broad s, 6H, $C^{11}(CH_3)_2$), 2.35 (broad s, 3H, $ArCH_3$), 2.82 (d, J = 7.5 Hz, 2H, $C^{21}H_2$), 3.15 (s, 6H, $NCH_3 + COOCH_3$), 6.77 (s) and 7.00 (s), together with 1H, C^2H. 7.15–7.60 (m, 3H, C^3H and C^5H Tos–NH Tos), 7.65–8.15 (m, 17H, 3 × ArP + C^2H and C^6H Tos). Found: C, 56.14; H, 5.42; N, 5.34; P, 3.74; S, 4.24. Calc for $C_{34}H_{38}N_2O_4SPI.CH_3CN$ (MW = 769): C, 56.17; H, 5.33; N, 5.46; P, 4.03; S, 4.16.

1 - *Tosyl* - 2(1 - *carbethoxy* - 1 - *methyl*)*ethyl* - 3,4,4 - *trimethylimidazolidine*(**25**)

Diisopropylamine (3 g, 30 mmol) was dissolved in 50 ml of freshly distilled THF. After the mixture had been cooled to − 78°, 22.5 ml of a 1.45 N solution of n-butyllithium in hexane (33 mmol, 1.1 equiv) was added carefully. After 5 min 3.5 g of ethyl isobutyrate (4.05 ml, 30 mmol) dissolved in 5 ml THF was added to the mixture. After stirring for another 10 min, 12 g of **18a** (30 mmol) was added, while vigorously stirring the mixture. Subsequently, the reaction mixture was allowed to warm to room temp. Following dissolution of the salt concentrated NH_4Cl solution was added (a few ml) and the mixture was concentrated under reduced pressure. The residue was filtered through silica gel with ethyl acetate as the eluent. After concentrating the filtrate the product was isolated as an oil which solidified and could be recrystallized from MeOH/H_2O, 2:1. Yield: 10 g of white crystals (87%); m.p. 83–85°. IR ($CHCl_3$): 1720 (s), 1350 (m), 1160 (s); PMR ($CDCl_3$): 0.81 (s, 3H, 1 C^4CH_3), 1.06 (s, 3H, C^4CH_3), 1.12 (s, 6H, $C^{11}CH_3$ and $C^{21}H_3$), 1.25 (t, J = 7.5 Hz, 3H, $COOCH_2\underline{CH_3}$), 2.21 (s, 3H, Ar CH_3), 2.39 (s, 3H, NCH_3), 3.05 (d, J = 11.5 Hz, 1H, C^5H), 3.62 (d, J = 11.5 Hz, 1H, C^5H), 4.06 (q, J = 7.5 Hz, 2H, $COO\underline{CH_2}CH_3$), 4.83 (s, 1H, C^2H), 7.27 (d, J = 8 Hz, 2H, C^3H and C^5H Ar), 7.73 (d, J = 8 Hz, 2H and C^6H Ar). Found: C, 59.74; H, 7.99; N, 7.28; S, 8.40. Calc for $C_{19}H_{30}N_2O_4S$: C, 59.70; H, 7.85; N, 7.34; S, 8.39).

Purine (**26**)

The salt **18a** (394 mg, 1 mmol) was dissolved in 7 ml of dry CH_3CN. During 1 hr, 110 mg (1 mmol) of 4,5-diaminopyrimidine was added to the mixture at 50–60°. After 1 night at 50–60° dilute sodiumbicarbonate solution was added and the mixture warmed to 80°, evaporated to dryness and the resulting brown tar was sublimed at 205° under reduced pressure (15 mm Hg). The product was recrystallized from ethanol containing a trace of toluene. Yield: 20 mg purine. M.p. 208–213°. IR: identical to Sadtler 14700; PMR: identical to Sadtler 4021 M.

Benzothiazole (**27a**)

The salt (197 mg) **18a** was dissolved in 3 ml of dry CH_3CN, 70 mg (0.65 mmol) of o-aminothiophenol was added and the mixture was refluxed for 4 hr. Subsequently water was added and the mixture was kept at reflux for another 30 min. Extraction with

ether and evaporating the ether fraction to dryness yielded a residue which was purified by chromatography (SiO_2, EtOAc/cHex 1:9). Yield: 54.2 mg (80%). IR: identical to Sadtler 2256.

Benzoimidazole (**27b**)

1,2-Diaminobenzene (172 mg, 1.6 mmol) and 591 mg of **18a** (1.5 mmol) were dissolved in 3 ml of dry CH_3CN and the mixture was refluxed for 3 hr. The mixture was hydrolyzed by adding dilute $NaHCO_3$ and refluxing for another half hour. After cooling to room temperature the mixture was extracted with chloroform. Drying over Na_2SO_4 and evaporating yielded a residue which was purified by chromatography (SiO_2, EtOAc). Yield: 92.2 mg yellow crystals; m.p. 165–169°. IR: identical to Sadtler 1685. PMR: identical to Sadtler 4270 M.

N-(2-Hydroxyphenyl)formamide (**27c**)

Salt **18a** (197 mg, 0.5 mmol) and 55 mg of 2-aminophenol (0.5 mmol) were dissolved in 1.5 ml of dry CH_3CN. The mixture was refluxed overnight and hydrolysed by adding $NaHCO_3$ soln. The mixture was purified by running it through a column containing Extrelut (Merck) and using ethyl acetate as the eluent. Yield: 44 mg; m.p. 123–126°. IR: identical to Sadtler 28942 (m.p. 122–125°).

Reactions of **18a** *with diaminoalkanes. Formation of* **28** (*n* = 3,4,5,6,9)

General procedure. The salt **18a** (1 mmol) and the diamine (1 mmol) were dissolved in CH_3CN (2 ml) and the mixture refluxed overnight. After cooling, the MeCN layer was decanted and the residue which consisted of the salt of **28**, treated with 50% NaOH and $CHCl_3$. After stirring the mixture for 2 hr, the $CHCl_3$ layer was separated, dried and evaporated. The product consisted of **28**. The products **28** were identified as their precursor salts. In a few cases the PMR spectra of cyclic amidines **28** could be determined. Yields of hydriodides **28** and the chemical shifts (DMSO-d_6) of their olefinic protons: n = 2 (41%); n = 3 (100%, 8.3); n = 4 (80%, 8.08); n = 5 (79%, 8.08); n = 6 (80%, 8.00); n = 9 (85%, 7.98).

1-*Tosyl-2-n-butyl-3,4,4,5,5-pentamethylimidazolidine* (**29a**)

The salt **18c** (422 mg, 1 mmol) was suspended in 10 ml of freshly distilled THF. The mixture was cooled to −100° using a mixture of ethanol and liquid nitrogen. At this temperature 1 equiv of n-BuLi in hexane was added and the stirred mixture was slowly allowed to reach room temp. After evaporation of the solvent the residue was purified by chromatography (SiO_2, EtOAc). Yield: 70 mg of oil (20%). IR ($CHCl_3$): 2980 (m), 1600 (w), 1345 (s), 1165 (s); PMR ($CDCl_3$): 0.42 (s, 3H, CCH_3), 0.86 (s, 3H, CCH_3), 1.25 (broad s, 6H, $C(CH_3)_2$), 0.70–1.70 (m, 9H, n-butyl group), 2.14 (s, 3H, NCH_3), 2.40 (s, 3H, $ArCH_3$), 3.95 (s, 1H, C^2H), 7.28 (d, J = 8 Hz, C^3H and C^5H Ar), 7.80 (d, J = 8 Hz, C^2H and C^6H Ar). The imidazolidine **29a** was also prepared by adding n-BuMgBr (from 29 mg Mg and 165 mg n-bromobutane) in THF and HMPT (2.4 mmol), to a suspension of **18c** (422 mg, 1 mmol) in THF. After stirring overnight a sat soln of NH_4Cl was added. Subsequently the mixture was extracted with ethyl acetate. The organic layer was washed with conc. NaCl solution and dried over Na_2SO_4. Evaporation of the solvent yielded a residue which was purified by chromatography (SiO_2/EtOAc). Yield: 98 mg of **29a** (28%). Spectral data identical to that described in the aforementioned.

1-*Tosyl-2-phenyl-3,4,4,5,5-pentamethylimidazolidine* (**29b**)

From 61 mg of magnesium (2.5 mmol) and 450 mg of bromobenzene (2.8 mmol) a soln of phenyl magnesium bromide in THF was made in the usual way.

This soln was added to a stirred suspension of 799 mg (2 mmol) of **18c** in 10 ml of THF. After stirring 5 hr at room temperature a 2% soln of HCl was added to the mixture, followed by $NaHCO_3$ solution in order to make the mixture basic. Subsequently it was extracted with ethyl acetate. The organic layer was washed with conc NaCl soln and dried over Na_2SO_4. Evaporation of the solvent yielded a residue which was purified by chromatography (Al_2O_3, CH_2Cl_2). Yield: 180 mg, recrystallized from ethanol. M.p. 124–127°. IR (KBr): 3000, 2970 (m), 1600 (w), 1350 (s), 1165 (s). PMR ($CDCl_3$): 0.72 (s, 3H, CCH_3), 0.93 (s, 3H, CCH_3), 1.38 (s, 6H, $C(CH_3)_2$), 1.89 (s, 3H, NCH_3), 2.30 (s, 3H, $ArCH_3$), 4.69 (s, 1H, C^2H), 6.69–7.65 (m, 9H, ArH).

Reaction of salt **18c** *with o-phenylenediamine, benzylamine and ethyl glycinate.*

o-Phenylenediamine (216 mg, 2 mmol) was added to a solution of **18c** (844 mg, 2 mmol) in 5 ml of CH_3CN and the mixture refluxed for 36 hr. After evaporation of the solvent, wet EtOAc was added whereupon **32** (41%) was obtained as insoluble material. From the solution **31a** was isolated after chromatography over a silica gel column (eluent: EtOAc). Yield: 57%. (**31a**) IR (KBr): 3460, 3380, 3200, 1620. PMR ($CDCl_3$): 2.36 (s, 3H, $ArCH_3$), 4.08 (s, 2H, NH_2), 6.40–6.70 (m, 5H, Ar–H + NHTs), 7.17 (d, 2H, J = (Hz, Ar–H), 7.60 (d, 2H, J = 8 Hz, Ar–H). Found: S, 12.23; Calc for $C_{13}H_{14}N_2O_2S$: S, 12.20.

Reaction of **18c** with benzylamine and ethyl glycinate, in the manner described above yielded the corresponded N-tosylated products **31b** (70%) and **31c** (73%), respectively. **31b**, IR (KBr): 3265, 1600, 1325, 1160. PMR ($CDCl_3$): 2.38 (s, 3H, $ArCH_3$), 3.92–4.20 (m, 2H, $ArCH_2$), 5.11 (broad s, 1H, NH), 7.10–7.40 (m, 7H, Ar–H), 7.72 (d, 2H, J = 8 Hz, Ar–H). **31c**, IR (KBr): 3270, 1742, 1328, 1165. PMR ($CDCl_3$): 1.18 (t, 3H, $CH_2\underline{CH_3}$), 2.42 (s, 3H, $ArCH_3$), 3.76–3.90 (m, 2H, CH_2N), 4.11 (q, 2H, $\underline{CH_2}CH_3$), 5.38 (broad s, 7H, NH), 7.31 (d, 2H, J = 8 Hz, Ar–H), 7.80 (d, 2H, J = 8 Hz, Ar–H).

Reaction of salt **18c** *with n-butyl bromide. Formation of* **30**

The same reaction conditions were employed in the formation of **29a**, except no HMPT was used. Yield: 151 mg (37%). IR($CHCl_3$): 3080, 1640, 1602, 1335, 1158. PMR ($CDCl_3$): 0.75–1.00 (m, 6H, $2\times CH_2CH_2CH_2\underline{CH_3}$), 1.05–1.08 (m, 24H, $2\times C(CH_3)_2$, $2\times -(CH_2)_3-$), 2.21 (s, 3H, NCH_3), 2.33 (s, 3H, $ArCH_3$), 2.78 (m, 1H, CH), 6.27 (s, 1H, NH), 7.19 (d, 2H, J = 8 Hz, ArH), 7.72 (d, 2H, J = 8 Hz, ArH).

Reaction of **18a** *with* 1,3-*dimethyl-6-aminouracil* (**33**, *R=Me, CH_2Ph) derivatives*

General procedure. Imidazolidine **19a** (0.5 mmol, 2 eq) was added to 0.5 mmol of the uracil derivative dissolved in a mixture of CH_3CN and acetic acid (2 ml) and the mixture allowed to stand at room temp. for 48 hr. At this stage all the aminouracil had been consumed. Evaporation of the solvents and precipitation of the residue from EtOAc gave **34a** and **34b** as foams. **34a**, PMR ($CDCl_3$): 2.86 (d, 6H, 2 NHMe), 3.32 (s, 6H, 2 NMe), 3.40 (s, 6H, 2 NMe), 3.42 (s, 2H, CH_2), 7.42–7.63 (m, 2H, 2 NHMe). **34b**, PMR ($CDCl_3$): 3.04 (s, 2H, CH_2), 3.32 (s, 6H, 2NMe), 3.46 (s, 6H, 2NMe), 4.27 (d, J = 7, 4H, $2NCH_2$), 7.35 (s, 10H, $2C_6H_5$), 7.75–8.05 (m, 2H, 2NH).

Reaction of **18a** *with indole*

The same reaction conditions were employed as in the case of the reaction of **18a** with 6-aminouracil derivatives. The reaction mixture was shown to contain **35**, which was identified by its PMR spectrum. PMR (CD_3CN): 4.18 (d, J = 1, C 2H, $-CH_2-$); no C_3-proton of indole was found in the spectrum. Further peaks in the spectrum corresponded to that of indole.

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