Conformational and Tautomeric Studies of Acylguanidines. Part 1. Synthesis, Ultraviolet Spectroscopy, Tautomeric Preference, and Site of Protonation in Some Model Compounds

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Six of the ten possible acylguanidine conformers have been prepared as model compounds in fixed form; all protonate on the imino nitrogen. The expected close u.v. resemblance between the cations is found for the major band near 200 nm but there are complications owing to a second band at higher wavelength and of very variable intensity whose origin is traced to an electronic transition involving σ-resonance. There is a clear distinction between the u.v. spectra of the 'through-conjugated' and 'cross-conjugated' free base forms, but with unexpected complications in certain cases which are believed to be due to the co-existence of near-planar and severely twisted species. There is a large tautomeric preference for the 'through-conjugated' forms, the extent of which is complicated by perturbations due to the molecular scaffolding. An attempt to allow for this and to predict the pK_a values for the nominal parent compounds leads to the conclusion that, for the *anti*-conformers, tautomeric ratio is *ca.* 300. Reasons are given for believing that these compounds are good models for related guanidinoheterocycles active as histamine H_2-receptor antagonists.

Guanidine derivatives such as the antihypertensive clonidine [1] and the diuretic amiloride (**6**) [2] have stimulated an interest in the medicinal chemistry of this structural unit that has recently been enhanced by the success of cimetidine and the high potency of tiotidine (**7**) as histamine H_2-receptor antagonists.[3] Such compounds display a bewildering array of conformational and tautomeric possibilities among which those actually preferred are known only qualitatively at the present time. Any attempt to develop hypotheses concerning detailed interactions at the receptor level requires a much more quantitative understanding, both to identify the major component and to assess the energetic penalty if some other sub-species is thought to be the active one. Such a task has recently been attempted, for the histamine H_2-receptor, by one of us.[4] That task provided the mainspring for this work.

Since the properties of minor sub-species are frequently unobservable, model compounds are required that embody their structures in fixed form. While the compounds considered above are diverse, all possess some electronegative group (*e.g.*, CN, phenyl, and the C=N of a heterocyclic ring) attached directly to the guanidine moiety. The need for a standard reference system led us to investigate the acylguanidines as possible models. This choice possessed the additional advantage that it allowed us to pursue a second objective: the development of guidelines, through the identification of spectroscopic properties characteristic of the various atomic groupings, for the assignment of structure even to quite distantly related compounds. This comes about since the carbonyl group is a sensitive probe or marker whose spectroscopy is well understood. The considerable success of this approach will be the subject of Part 2,[5] wherein the infrared, Raman, and carbon-13 n.m.r. spectra will be analysed and discussed. It turns out, also, that carbonyl was a good choice in terms of tautomeric ratio; that in favour of the through-conjugated † tautomer written for the guanidinothiazole (**8**) [6] closely matches those for the acylguanidines to be discussed below. This circumstance lends weight to the view that deductions drawn for the acylguanidines are likely to remain valid for the compounds they are intended to model.

For any guanidine derivative in which the double bond is fixed in position, there are five different bonds that could carry a carbonyl substituent. For each bond there are two planar conformations, *syn* and *anti*, of the carbonyl group. Introduction of suitable rings and substituents allows the ten possible acylguanidine atomic groups (Figure 1) to be fixed (**1*a***, **2*a***, **3*a***, **4*a***, **5*s***) or strongly preferred (**1*s***, **2*s***, **3*s***, **4*s***, **5*a***) while the protonated species take up ***a*** or ***s*** conformations in line with those of the neutral species, except that (**5*a***) would probably join the ***s*** category of cation. No clear differences have yet been seen between the two protonated conformations, but they are included in Figure 1 for completeness. In this paper we discuss the synthesis, u.v. spectra, pK_a values, and tautomeric equilibria of those acylguanidines we have been able to prepare in fixed forms, along with certain tautomerically or conformationally mobile compounds whose structures may be assigned by use of the criteria developed herein.

Results and Discussion

Synthesis.—The type (**1*s***) compounds (**9**)—(**12**) were prepared by reaction of the appropriate ester or acid chloride with the guanidine.

2-Amino-2-imidazoline (**13**) has been shown [7] to react with ethyl acrylate to give exclusively the type (**1*a***) product (**17**). The other possible product from this reaction, (**24**), was prepared unequivocally by ring closure of the 3-guanidino acid (**26**). This was simply achieved by refluxing in mineral acid, an improvement on the two-step procedure.[8] It is interesting that the guanidinium ion is sufficiently nucleophilic to react with the protonated carboxylic acid group. Cyclisation also occurred with dicyclohexylcarbodi-imide in the presence of toluene-*p*-sulphonic acid. Ethyl acrylate and 2-iminohexahydropyrimidine (**14**) gave (**18**).

The ring *N*-methyl derivatives (**15**) and (**16**) reacted similarly to give only the through-conjugated products (**19**) and (**20**). 2-Methylamino-2-imidazoline (**21**) gave only the type (**3*a***) acyl

† Throughout this paper we shall refer to compounds as *through-conjugated* when imino-nitrogen is adjacent to carbonyl and as *cross-conjugated* otherwise. It is not intended that either expression indicates a greater or lesser degree of conjugation than the other.

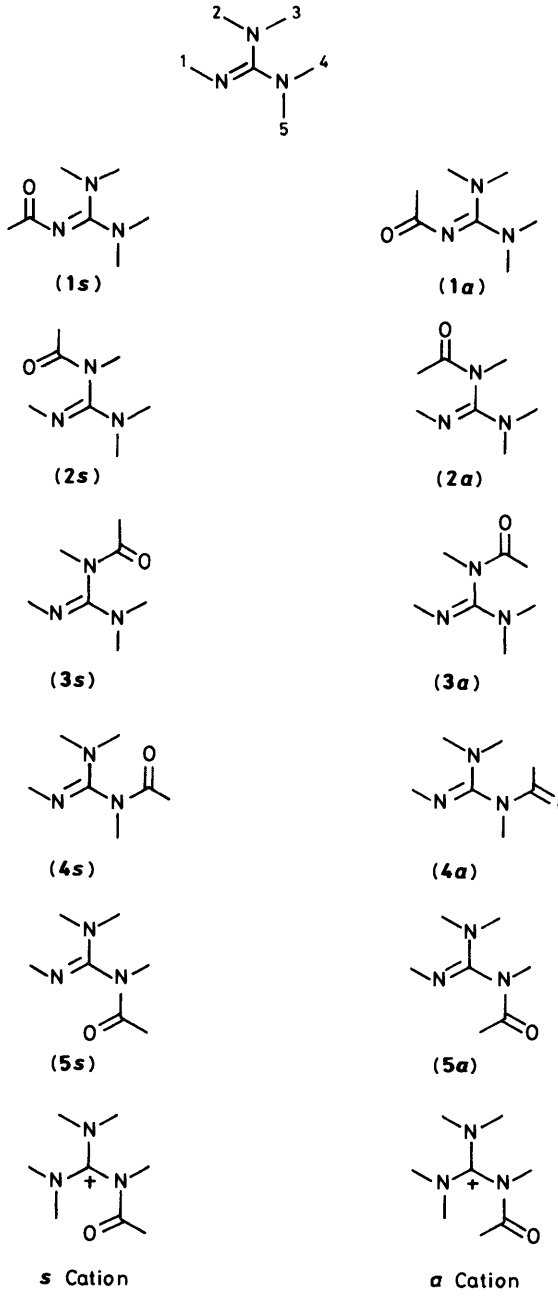
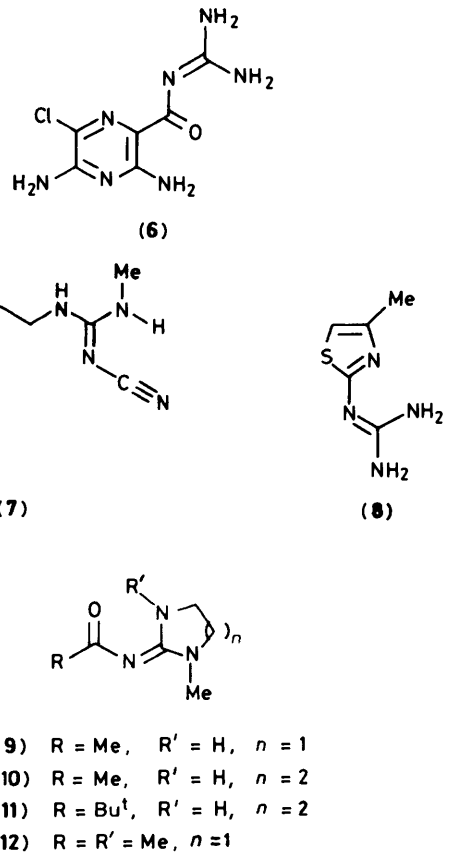


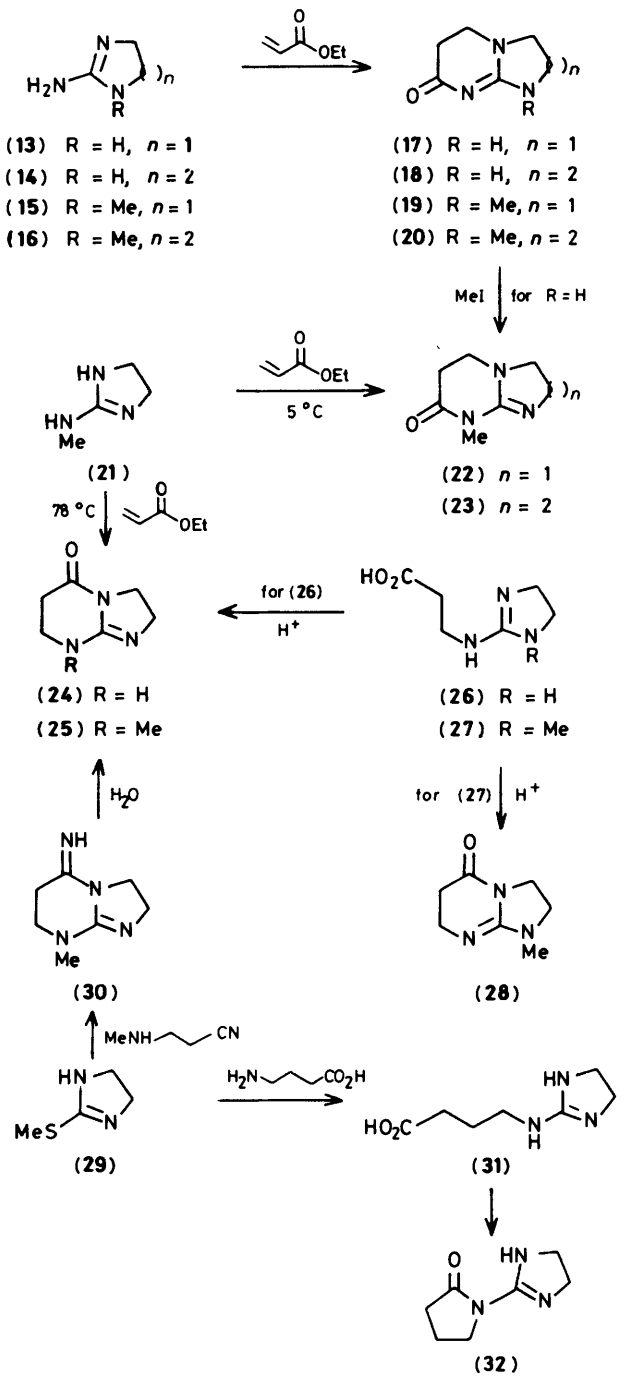
Figure 1. The ten types of acylguanidine and two cations



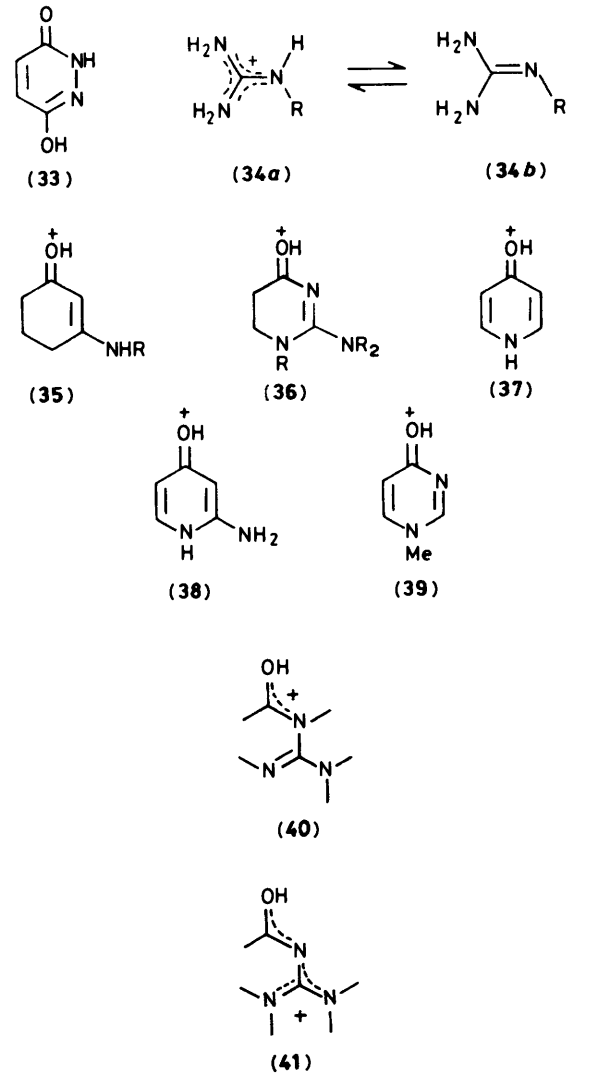
guanidine (**25**) in refluxing ethyl acrylate. However, when the reaction was run in ethanol at 5 °C, it gave a 61% (crude) yield of (**25**) accompanied by 23% of compound (**22**). The same compound was obtained (80%) when (**17**) was boiled with iodomethane, confirming its structure. Similarly (**18**) gave (**23**). Compound (**25**) was best prepared by hydrolysis of the isolatable imine (**30**), Scheme 1, a reaction which confirmed its structure. The precursor (**29**) to this imine was also used, by reaction with γ-aminobutyric acid, to give the pyrrolidone (**32**), which was formed from the ethyl ester of (**31**) by spontaneous cyclisation.[7] The type (**2a**) compound (**28**) was prepared by ring closure of the acid (**27**) in 60% hydrobromic acid.

Site of Protonation.—Since amides,[9] vinylogous amides,[10] and heterocycles such as pyridones[11] protonate on oxygen almost without exception, it is necessary to establish the site of protonation for the acylguanidines discussed here. These differ from the above mentioned types in that nitrogen lone pairs within the σ-system are available for protonation, so that it is not necessary to protonate the inherently less basic oxygen atom, let alone amino nitrogen with its concomitant disruption of the π-system. While protonation on imino nitrogen is therefore inherently reasonable for all the present compounds, the existence of maleic hydrazide (**33**) as an exception to this rule[12] imposes the need for some attempt at proof.

We shall present in Part 2[5] unequivocal i.r. and Raman evidence for nitrogen protonation in the solid state, as previously shown for amiloride (**6**) by *X*-ray crystal-structure determination.[2] The u.v. spectra to be discussed below also provide substantial though not unequivocal evidence for nitrogen protonation in aqueous solution. In addition, two sorts of circumstantial evidence can be found in the literature. Charton[13] has shown that the pK_a values of substituted guanidines (**34**) fit a single relation with σ_I which applies equally to those compounds, *e.g.*, acetylguanidine, for which an alternative site of protonation might be possible, and to those (the majority), *e.g.*, phenylguanidine, for which it is not. The absence of any perturbation for the former class must mean, at worst, that *N*- and R-protonation are comparable. (On the same reasoning, as Charton observes,[13] deprotonation must always involve the same nitrogen atom; this point has relevance to the question of tautomeric preference to be discussed below.) The second type of evidence comes from an admittedly approximate estimation of pK_a values for rival cations. Several enaminones of type (**35**) possess[10] pK_a values *ca.* 3.1; we need to attempt an estimate for cation (**36**). We note firstly that the pK_a values of (**37**)[12] and (**35**) are very little different, and that the extra amino group of (**38**) raises its pK_a by *ca.* 2 units.[12] The effect of the added imino



Scheme 1.



nitrogen in (**36**) is much more difficult to estimate. Ideally it might be obtained from such a compound as (**39**) if this were to *O*-protonate, but it does not; protonation of the amidine unit is preferred [12] (which is where this argument began). However, one may note that the second nitrogen atom of pyrimidine reduces its pK_a by *ca.* 4 units relative to pyridine. While that may over-estimate the effect in the present context, it seems on balance probable that the (*O*-protonated) acylguanidines will be weaker bases than the enaminones; *i.e.*, $pK_a < 3$. Since the weakest base here studied has $pK_a > 5$, it seems unlikely that any appreciable *O*-protonation can occur. Consistently, we present evidence in the next section, and in Part 2,[5] that the carbonyl groups of acylguanidines are on balance less electron-rich than the enaminones. This question will be further discussed on another occasion.[14]

The above arguments apply in their pure form only to the through-conjugated types (**1***a* and *s*). For the remaining, cross-conjugated types there exists the additional argument that *O*-protonation confines cationic resonance to the amide unit, as in (**40**), and does not permit involvement of the amidine moiety as in the through-conjugated cation (**41**). In addition these compounds are stronger bases, with $pK_a > 7$. This greater basicity is intimately linked with the question of tautomeric preference, which will be considered later.

Ultraviolet Spectroscopy.—With one important caveat to be considered below, the u.v. spectra for the free-base forms of the through-conjugated (**1***a* and *s*) types are distinguished from the remainder by the presence of a single, strong band near 230 nm. This is illustrated on Figure 2 for (**9**) and on Figure 3 for (**17**). By contrast, the cross-conjugated types possess their strongest band close to 200 nm with, for the most part, only relatively weak absorption at higher wavelengths. This distinction is in line with the differing types of dipolar resonance structure that can be written in each case, *i.e.*, (**42**) and (**43**), respectively. It also serves to identify the prototropically mobile compounds (**17**) and (**18**) as unequivocally in the through-conjugated form, as is

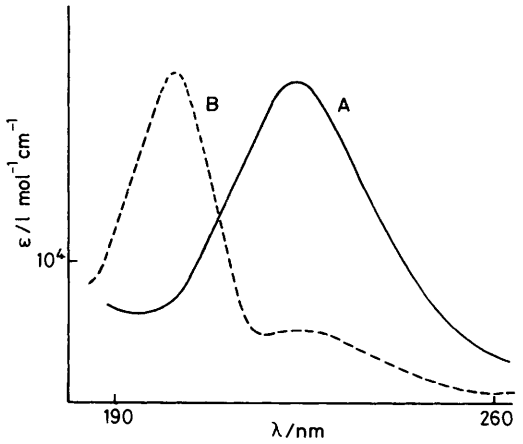


Figure 2. U.v. spectra of compound (**9**) in aqueous solution: A, at pH 9.9 and B, at pH 3.3

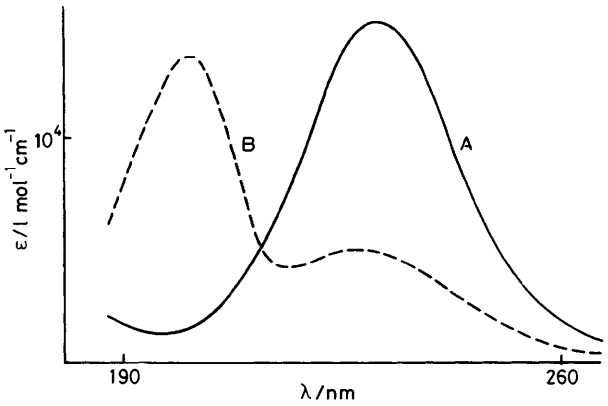
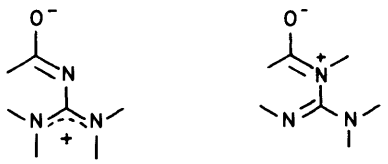


Figure 3. U.v. spectra of compound (**17**) in aqueous solution: A, at pH 10.1 and B, at pH 3.4



(**42**) (**43**)

also supported by their pK_a values and, in weakly polar solvents, by their i.r. spectra.

This u.v. evidence suggests that the through-conjugated types are in general less conjugated as a class than the enaminones. The latter show[10] $\lambda_{max.}$ close to 300 nm (log ε 4.2—4.5). Presumably the highly electronegative imino nitrogen atom, while formally equivalent to CH, acts as an electron sink and reduces conjugation through to the carbonyl oxygen.

The principal caveat concerns compounds (**10**) and (**11**). Here the neutral forms in water (see Figure 4) show clear evidence for the co-presence of two or more species. Our initial inclination was to postulate the coexistence of cross- and through-conjugated species, but the pK_a data rule out this possibility (see below). We now believe that these ill-defined spectra reveal the presence of highly twisted conformers such as *B* in addition to the expected near-planar conformer *A*. (These structures and those of 2-acetylimino-1,3-dimethylimidazolidine and its

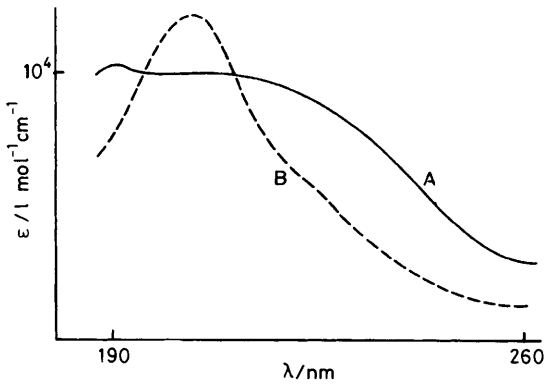
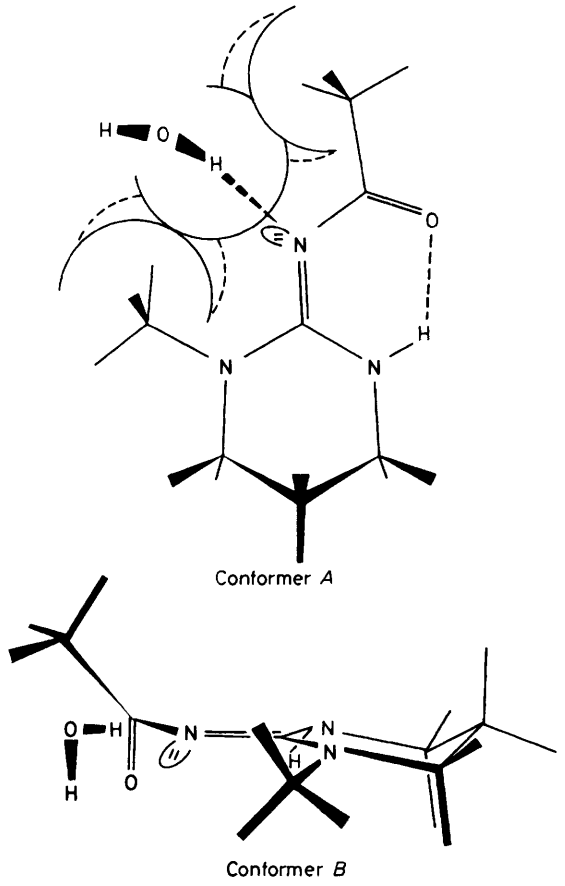


Figure 4. U.v. spectra of compound (**10**) in aqueous solution: A, at pH 10.1 and B, at pH 3.3. [*N.b.* compound (**11**) gives very similar spectra]



protonated form are presented in greater detail as Supplementary Information.*) This deformation in water, a powerful hydrogen-bond donor, would be helped by adverse factors in *A* as well as other factors which might actually favour *B*. Some of these have been revealed by a study using computer graphics with manual optimisation of bond angles and van der Waals overlap. Both the donor and the acceptor atoms of the intramolecular hydrogen bond in *A* possess far from the ideal geometry for such interactions, whereas the more open structure *B* will allow strong hydrogen bonding of solvent to carbonyl

* *Supplementary data available* (No. SUP 56257, 5 pp.): atomic coordinates, bond lengths and angles. See *J. Chem. Soc., Perkin Trans. 2*, Instructions for Authors, section 4.0 (January Issue).

Table. U.v. and pK_a data[a]

Compound	pK_a	$\lambda_{max.}$/nm (log ε) $H_2O(BH^+)$	$H_2O(B)$	MeOH	MeCN	C_6H_{12}
(**9**)	6.72	200 (4.10)				
		226 (3.64)	230 (4.16)	233 (4.23)	238 (4.25)	237 (4.29)
(**10**)	7.24	203 (4.12)	207 (3.98)	*225* (4.00)		
		225 (3.75)	*235* (3.80)	236 (4.13)	241 (4.27)	242 (4.36)
(**11**)	6.97	204 (4.05)	209 (4.00)			
		220 (3.90)	*235* (3.85)	241 (4.39)	242 (4.40)	243 (4.36)
(**12**)	5.25	200 (3.87)				
		241 (3.78)	222 (4.00)	226 (4.09)	233 (4.14)	237 (4.10)
(**17**)	5.80	201 (4.20)			*220* (4.00)	
		225 (3.45)	222 (4.16)	225 (4.11)	237 (4.10)	230[b]
(**18**)	6.79	203 (4.20)				
		225 (3.59)	224 (4.19)	*228* (4.13)	219 (3.99)	
			240 (4.05)	238 (4.16)	245 (4.22)	
(**19**)	5.21	204 (4.15)				
		234 (3.58)	231 (4.25)	233 (4.30)	235 (4.28)	236[b]
(**20**)	6.72	207 (4.28)				
		230 (3.86)	233 (4.37)	239 (4.31)	245 (4.29)	
(**22**)	7.98	208 (4.20)	210 (4.06)	208 (4.04)	207 (4.07)	
		235 (3.45)	240 (3.57)	235 (3.56)	235 (3.68)	
(**23**)	9.49	209 (4.25)	203 (4.04)	207 (4.05)	[c] (>4)	
		235 (3.60)	242 (2.77)	235 (3.37)	240 (3.72)	
(**24**)	8.36	196 (4.24)	195 (4.25)	[c] (>4)	198 (3.96)	
		221 (4.37)	224 (4.28)	*235* (3.63)	225 (3.76)	
(**25**)	8.14	194 (4.23)	194 (4.10)	213 (4.08)	210 (4.06)	
		220 (4.24)	222 (4.30)	*235* (3.84)	*235* (3.86)	
(**28**)	8.56	199 (4.22)	196 (4.28)	[c] (>4)	*208* (4.35)	
		217 (4.23)	*215* (4.13)	*235* (3.25)	215 (4.36)	
(**32**)	9.43	[c] (>4)	[c] (>4)	[c] (>4)	[c] (>4)	
		238 (2.89)	238 (3.22)	*242* (2.95)	235 (3.52)	

[a] Shoulders are italicised. [b] Too insoluble for accurate intensity. [c] Below 200 nm.

and weak but significant interactions with the now partially pyramidalised ring nitrogen atoms. Curiously, imino nitrogen is shielded from solvent nearly as badly in *B* as in *A*, but the looser packing of the atoms in *B* will allow greater vibrational and rotational freedom, which will result in increased entropic stabilisation of this state. In addition, some angle strain is present in the exocyclic portion of *A* which is relieved by twisting, and loss of through resonance will in part be compensated by overlap of the carbonyl π-system with the imino lone pair, as emphasised by the way in which *B* is drawn.

The presence of a twisted form such as *B* would of course be consistent with the extra intensity at low wavelengths visible in Figure 4. (This is *not* caused by decomposition: see Experimental section.) Species *B* would be expected to be of comparable basicity to *A* since (*a*) carbonyl can still exert its full *inductive* force and (*b*) partial resonance of the imino lone pair with the carbonyl group should reduce its availability for protonation.

It is consistent with this explanation that the phenomenon virtually disappears in methanol and is absent not only in non-polar solvents but in the proton acceptor acetonitrile (Table). It is also not shown by the imidazolines (**9**) and (**12**) in any solvent. The erratic behaviour of solvent effects in other compounds may indicate changing mixtures of conformers or hybridisation states, but on a much smaller scale than those above. Almost certainly, a similar explanation will fit the similar u.v. phenomena found for some other crowded acylguanidines by Rapoport and co-workers.[15] In terms of the essential purpose of this investigation, it may be noted that the energetic penalty against loss of planarity for the heterocyclic guanidines may be considerably less than that to be expected on resonance arguments alone.

The u.v. spectrum of each cation (Table) shows a strong, fairly constant, band near 200 nm accompanied by one at 220—240 nm of much more variable appearance.* The former band is close to that generally dominant in the free-base forms of the cross-conjugated types, which is reasonable since both possess amino and not imino nitrogen adjacent to carbonyl. Hence electronic reorganisation during protonation of the through-conjugated types is expected to be more extensive, as these u.v. spectra clearly show. The second absorption ranges in intensity from a barely discernible shoulder, *e.g.*, in (**10**) and (**11**), through a weak but definite band in the majority of cases, to a well resolved peak of equal or even greater intensity than the first, as in (**24**), (**25**), and (**28**). This sequence can be followed through Figures 4, 3, 2, and 5. Since these last compounds possess the cross-conjugated structure for which, as seen above, *O*-protonation is even less likely than elsewhere, some other explanation must be found for this phenomenon.

We believe that the changes in $\lambda_{max.}$ and ε shown by this second cation band are consistent with the presence of excited states such as that shown for (**25**) in Scheme 2. Because the amidine moiety becomes much more acidic in the excited state, we suggest that the already strongly hydrogen-bonded proton allows a higher probability for this transition than does an alkyl group. This will explain the observed order of extinction coefficient, as (**24**) > (**25**), (**28**) ≫ (**22**). The type of resonance represented by *E* is important only when NH is antiperiplanar to a strong electron acceptor, hence the weakness of this transition, *e.g.*, in (**22**). This σ-bond–no-bond resonance has

* The u.v. data of Matsumoto and Rapoport[15b] are largely omitted from our discussion, because our results for compound (**24**) differ substantially from their data for the same compound.

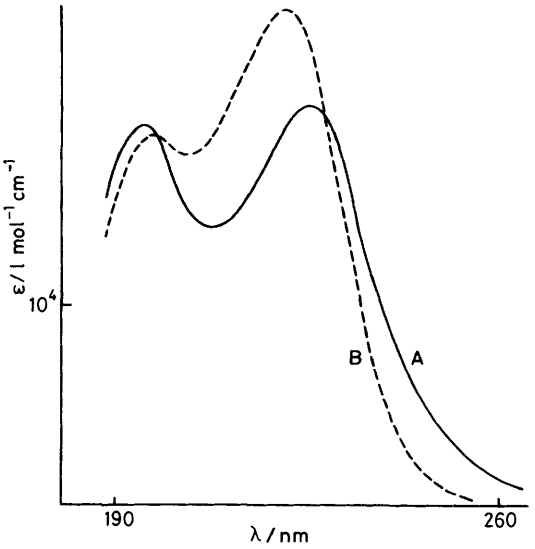
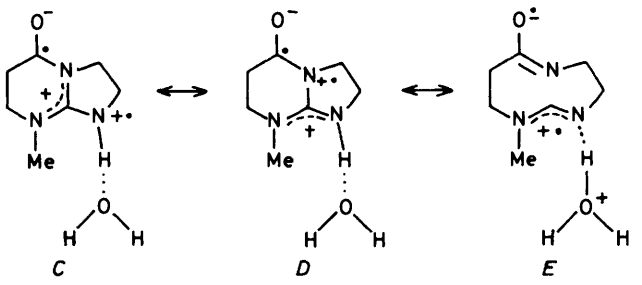


Figure 5. U.v. spectra of compound (**24**) in aqueous solution: A, at pH 10.0 and B, at pH 3.3

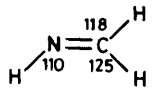


Scheme 2.

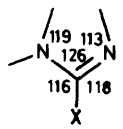
been discussed by Baldwin and Norris[16] and also has consequences for the i.r. spectroscopy, as will be seen in Part 2.[5] The prominence of this transition for (**12**) cation may be due to twisting about the amide–amidine CN linkage, which is another way of reducing its bond order and so making this a favoured process. Such twisting is compatible with anomalously low i.r. (Part 2) and u.v. intensities for the free base. Similar but smaller distortions may occur elsewhere. It is also possible that an essentially similar phenomenon, but this time involving neutral water, is responsible for the longer wavelengths transition of certain *free-base* forms (Table) among which (**24**) and (**25**) are once again particularly prominent (Figure 5). We shall present evidence in Part 2 that the consequences of σ-resonance are also visible in the *vibrational* spectroscopy of these two compounds.

Tautomeric Preference.—Figure 1 demonstrates the formal relation of the through-conjugated and cross-conjugated free bases to the cation common to each (no distinction between *a* and *s* cations has been detected in this study). A simple qualitative argument, given by Charton,[13] would suggest that deprotonation of the cation should take place preferentially from that nitrogen atom adjacent to the most electronegative substituent, as shown for (**34***a*), to give therefore the through-conjugated tautomer. Our results bear out that hypothesis.

How quantitatively it is borne out is, however, open to argument. In addition to large p*K* differences between tautomers, there are also large p*K* differences between the same tautomer when the context changes, most obviously as a function of ring size. There is even an appreciable difference



(**44**)



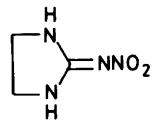
(**45**)

between (**25**) and (**28**). Our original hope, that effects due to the scaffolding would be small and easily interpretable, has clearly not been fulfilled. In terms of the energetic factors in drug-receptor interaction to which this study is related, it is important to make sense of these differences. That task is currently being attempted in a comprehensive manner, which takes into account many more variables, and structures, than are relevant in the context of these compounds alone.[14] The following discussion is a simplified but not misleading account of the factors that appear to apply in the present case.

The geometry of methyleneimine (**44**) has been determined by microwave spectroscopy[17] and *ab initio* calculation[18] with results that closely agree. The angles derived from the microwave study are shown. These show an internal bond angle at imino nitrogen much less than normal at sp^2-carbon, and a marked asymmetry of the angles around carbon; this result is substantiated by many more complex structures.[14] For the amidine unit (**45**), where X is a substituent of relatively slight electronic demand, the same analysis[14] predicts the desired bond angles shown. Here the π-donor nitrogen already possesses almost the trigonal geometry which both will desire on protonation. It is clear that, if this amidine unit be incorporated into a ring, either cation or free base may be strained, according to ring size. These considerations underlie much of the argument that follows.

On i.r. evidence (Part 2),[5] (**24**) in weakly polar solvents exists overwhelmingly in the form corresponding to (**25**). This tautomeric preference is at first sight surprising since it is contrary to expectation based on the classical work of Brown *et al.*[19] on the relative stabilities of *endo*- and *exo*-double bonds in 5- and 6-membered rings. However, as seen above, imino nitrogen is a different case; it could better fit a 5-membered ring (mean bond angle 108°) than a 6-membered ring (mean bond angle 120°). In solvent water the tautomeric preference of (**24**) is much less marked but the 5-*endo* double bond is still preferred since the aminoimidazoline (**25**) is a weaker base, *i.e.*, a more stable tautomer,[12] than the iminoimidazoline (**28**). Their pK_a difference implies that about 70% of (**24**) should exist in water as the tautomer corresponding to (**25**). Qualitatively, its free-base u.v. spectrum (Figure 5) possesses just about the ratio of intensities that might be deduced from (**25**) and (**28**) on this basis. The reduced tautomeric ratio in water is in part the consequence of strong hydrogen bonding at the imino lone pair (incipient protonation and angle expansion). Since the cations are identical, complications from this source do not arise.

They do, however, when it comes to comparing ring size generally. Protonation of the guanidine unit leads to desired bond angles of about 120° not only on the central carbon atom but on all three nitrogen atoms attached to it; furthermore, the cation is expected to be less deformable than the free base. Hence considerable strain will be generated in cations that incorporate 5-membered rings. The effect on pK_a will be greatest for compounds containing endocyclic C=N since, as seen above, this is positively favoured for 5-membered rings, but it still operates for exocyclic imino functions.[14] These factors operating against cation formation in 5-membered rings are reinforced by a positive factor in favour of larger ring cations whose importance has recently become clear from high-level MO calculation. In organic cations generally, as much charge as possible is distributed around the periphery; most of the positive



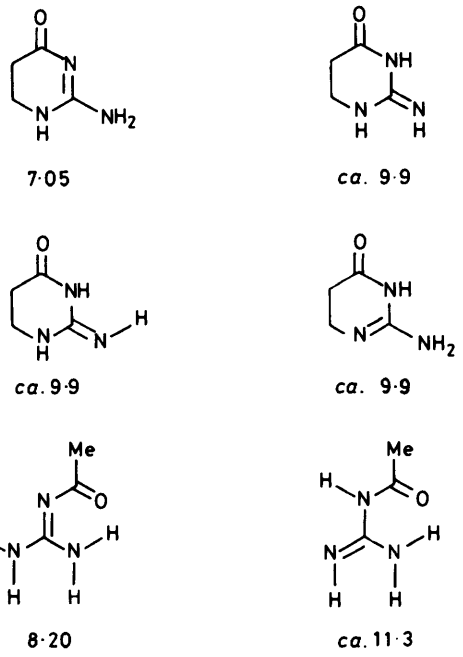
(46)

charge in amine cations is to be found on carbon and hydrogen.[20] While the resultant base-strengthening effect of alkyl groups has its greatest impact in the gas phase,[21] sufficient can remain even in aqueous solution to be important. In the present case, the charge repulsion operative between the adjacent CH_2 units of the imidazolium-type cations can be largely but not entirely relieved in the trimethylene unit present in 6-membered rings; furthermore the nitrogen atoms are better separated, which must also help. We estimate this overall effect as responsible for an increment of pK_a *ca.* −0.3 for 6-membered rings, *e.g.*, (**23**), while the base-weakening effects of *endo*- and *exo*-cyclic C=N in 5-membered rings are estimated as pK_a *ca.* −1.8 and −1.2 respectively;* these effects however vary with the nature of the substituents and are those which appear appropriate, barring compound (**12**), in the present case. [As an example of another case the strongly electron-attracting nitro group of (**46**) reduces the *exo*-5-membered ring effect to −0.5 pK_a units.[14]]

Alkyl groups on imino nitrogen are considered to be base-strengthening by 2- to 3-fold, while alkylation at nitrogen in general leads to complications in that new *peri*-type interactions are necessarily generated; either with another *N*-alkyl group, or with a solvated NH group, or with a solvated *N*-lone pair. The results of such interactions can be large and unexpected as seen already for the cases of (**10**) and (**11**), but more typically the effects on pK_a range from zero to −0.7.

The very low pK_a of (**12**) is abnormal, the result of crowding of a different sort than in (**10**) and (**11**). While on spectroscopic evidence this is relieved for the free base in some manner which avoids serious distortion of the conjugated system (we suspect a progressive helical twisting of the whole conjugated unit), the cation distorts most easily by rotation about the amide to imidazolium bond, with consequential reduction in charge sharing by the amide group and reduced basicity.

From the tautomer pairs (**20**) and (**23**), (**19**) and (**22**), and (**9**) and (**32**), one can deduce tautomeric ratios in favour of the through-conjugated forms of highly alkylated derivatives. These pK_T values work out at 2.71, 2.77, and 2.71, respectively. Even allowing for the possible perturbations discussed above, and some others,[14] the results from the first two pairs represent an impressive degree of agreement.† The near identity of the value in the third case is judged to be a consequence of the open nature of (**32**) which results in a base-weakening effect relative to the more strongly intramolecularly hydrogen-bonded and compact structure of (**9**); the corresponding pK_T for the parent system is assigned a value of 3.1.[14]



7·05 *ca.* 9·9

ca. 9·9 *ca.* 9·9

8·20 *ca.* 11·3

Figure 6. Through-conjugated tautomers and alternatives with experimental pK_a values[22] and estimates[14] (to ± 0.3)

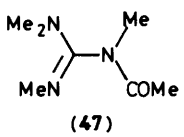
A more wide-ranging consideration of many possible factors[14] results in the picture summarised in Figure 6. Here the pK_a values for the 'through-conjugated' tautomers are experimental[22] whereas those for their alternatives are our estimates.[14] Again pK_T remains close to 3 in both *syn*- and *anti*-forms. An interesting point which does emerge, however, is the much higher basicity of the *syn*-forms in the absence of strain. While hydrogen bonding may play some part in this difference, an important factor is probably the much larger electron-withdrawing effect generated by carbonyl in the *anti*-form owing to its dipole alignment. This conformational effect is not well parameterised by existing σ-scales[23] but there is ample evidence for it at least in the general context of pK_a values.[14]

Summary and Conclusions

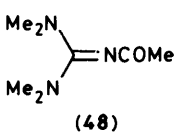
So far as these are relevant to drug-receptor binding, they may be stated as follows. (1) The through-conjugated forms of unstrained type ***a*** acylguanidines are favoured by a factor of about 300.‡ Inside a given conformation, *syn* and *anti*, it is probable that all minor sub-species [except (**5***s*)] are disfavoured by similar margins.[14] (2) There is a considerable preference for the *syn* form of the through-conjugated tautomer, where this is possible. We shall present evidence in Part 2[5] that a major factor here, at least in weakly polar solvents, is repulsion between the carbonyl and imino nitrogen lone pairs in the *anti* form. (3) Basicity, irrespective of conformation, is sharply reduced in 5-membered rings. There is some evidence that differences in basicity between open-chain and 6-membered cyclic guanidines are two-fold or less. (4) Planarity of the entire unit is preferred on resonance grounds. Nevertheless some latitude is allowed to the free-base forms since other factors

* These increments are designed to yield the pK_a values of hypothetical 'strain-free' *seco*-systems which have methyl groups in place of the alkylene chain. This procedure allows necessary differential resonance effects between $-NH_2$, $-NHAlk$, and $-N(Alk)_2$ to be applied.[14] These resonance effects are not those expected from literature precedent:[23] $\Delta\sigma_R^+$ values (assuming constant σ_I) are estimated[14] as $-NH_2 \longrightarrow -NHAlk$, −0.04; $-NHAlk \longrightarrow -N(Alkyl)_2$, +0.02.

† These values are much higher than the pK_T *ca.* 1.6 deducible from (**47**) and (**48**) as studied by Matsumoto and Rapoport;[15b] but these latter compounds are certainly very far from planar in the free-base forms and their cations must be very strained.



(47)



(48)

‡ This number incorporates the necessary statistical correction based on the existence of *three* cross-conjugated forms of approximately equal basicity.

(dipolar effects, hydrogen bonding to solvent) can help to compensate; lack of planarity, when it occurs, will take whatever form is best able to optimise all factors. However, much less compensation is possible for cations, whose stability in consequence will be sharply reduced. (5) Most or all of these conclusions can probably be generalised to the heterocyclic guanidines. While tautomeric ratio in substituted guanidines is some function of basicity,[14] that of most heterocyclic guanidines of interest lies[6,14] squarely across the range considered here. Hence the choice of these compounds as models stands vindicated.

Experimental

N.m.r. spectra were recorded on Perkin-Elmer R12, Varian 90 or Joel JNM 90 Q instruments, i.r. spectra on Perkin-Elmer 457 or Perkin-Elmer 267 spectrophotometers, and mass spectra on an AEI MS902 mass spectrometer.

U.v. spectra were recorded on a Pye Unicam SP8-100 spectrophotometer at *ca.* 10^{-5}M, generally within a few minutes of preparing the solution, and sometimes at once. This precaution was essential for the free-base from of cross-conjugated compounds in water, which are susceptible to alkaline hydrolysis. Compounds (**23**) and (**28**), investigated as typical, gave half-lives for hydrolysis at pH 10 of *ca.* 30 min whereas the through-conjugated compounds (**10**) and (**11**) showed no appreciable reaction in this time and none of these compounds appeared to hydrolyse appreciably at pH 3. Buffer pH values were adjusted to ensure >97% of free base or cationic forms.

pK_a Values were determined at 23 °C for salts against 0.05M-KOH on a Metrohm Potentiograph E436 (titration speed 3) using *ca.* 10^{-4}M-samples in distilled water (30 ml). Solutions were protected by a blanket of nitrogen and were stirred for *ca.* 10 min, at pH 2—3, before titration to remove dissolved carbon dioxide. Replication (2—4 determinations per compound) established reproducibility at ±0.06 pK units. Variation in titration speed had no effect.

U.v. and pK_a data are summarised in the Table.

M.p.s are uncorrected.

2-*Acetylimino*-1-*methylimidazolidine* (**9**).—2-Amino-1-methyl-2-imidazoline hydrobromide (18.0 g, 0.1 mol) was added to a solution of sodium (2.3 g, 0.1 mol) in ethanol (60 ml) and stirred for 1 h. The product was filtered, the alcohol evaporated, and the residue dissolved in ethyl acetate (100 ml) and refluxed overnight. The solution was cooled, filtered, and evaporated to give the *amide* (10.2 g, 76%), m.p. 121 °C (from butanone) (Found: C, 51.0; H, 8.2; N, 29.8. $C_6H_{11}N_3O$ requires C, 51.0; H, 7.9; N, 29.8%); $\nu_{max.}$(Nujol) 3 320, 1 590, and 1 530 cm^{-1}; $\delta_H(CDCl_3)$ 8.80 (1 H, s, NH), 3.55 (4 H, m, 2 × NCH_2), 2.95 (3 H, s, NMe), and 2.11 (3 H, s, COMe).

2-*Acetylimino*-1-*methylhexahyropyrimidine* (**10**).—2-Amino-1-methyl-1,4,5,6-tetrahydropyrimidine hydrobromide[24] (19.4 g, 0.1 mol) by the same technique (2.5 h reflux) gave the *amide* (10.1 g, 65%), m.p. 111—113 °C (from butanone) (Found: C, 54.2; H, 8.5; N, 27.0. $C_7H_{13}N_3O$ requires C, 54.2; H, 8.5; N, 27.2%); $\nu_{max.}$(Nujol) 3 190, 1 595, and 1 575 cm^{-1}; δ_H([$^2H_6$]DMSO) 3.28 (4 H, t, 2 × NCH_2), 3.15 (1 H, s, NH), 2.97 (3 H, s, NMe), 1.86 (2 H, m, CH_2), and 1.85 (3 H, s, COMe).

2-(2,2-*Dimethylpropanoyl*)*imino*-1-*methylhexahydropyrimidine* (**11**).—A solution of 2-imino-1-methylhexahydropyrimidine [from the hydrobromide[24] (38.8 g, 0.2 mol) and sodium methoxide] in dichloromethane (120 ml) was cooled on an ice-bath. Pivaloyl chloride (22 ml, 0.18 mol) in dichloromethane (120 ml) was added dropwise with stirring with the temperature kept below 25 °C. The final solution was refluxed (1 h). The solvent was evaporated and the residue extracted with boiling butanone (2 × 125 ml) which was reduced in volume to give the *amidopyrimidine hydrochloride monohydrate* (19.6 g, 43%), m.p. 102—103 °C (from butanone) (Found: C, 47.7; H, 9.2; Cl, 13.9; N, 16.7. $C_{10}H_{22}ClN_3O_2$ requires C, 47.8; H, 8.8; Cl, 14.1; N, 16.7%); $\nu_{max.}$(Nujol) 3 180, 1 706, and 1 671 cm^{-1}; $\delta_H(CDCl_3)$ 9.93 (1 H, s, NH), 3.63 (4 H, t, 2 × NCH_2), 3.12 (3 H, s, NMe), 2.15 (2 H, q, CH_2), and 1.34 (9 H, s, 3 × Me). A methanolic solution, by ion exchange, gave the *free base* (96%), m.p. 92—93 °C (from light petroleum, b.p. 80—100 °C) (Found: C, 60.8; H, 9.9; N, 21.7. $C_{10}H_{19}N_3O$ requires C, 60.9; H, 9.7; N, 21.3%); $\nu_{max.}$ ($CHCl_3$) 1 580 cm^{-1}; δ_H ($CDCl_3$) 3.32 (4 H, t, 2 × NCH_2), 3.12 (3 H, s, NMe), 1.95 (2 H, q, CH_2), and 1.16 (9 H, s, 3 × Me).

2-*Imino*-1,3-*dimethylimidazolidine*.—A solution of cyanogen bromide (5.0 g, 47 mmol) in methanol (12 ml) was added dropwise to a stirred solution of *sym*-dimethylethylenediamine (5 ml, 47 mmol) in methanol (12 ml) while the temperature was maintained below 20 °C. Stirring was continued at room temperature (1 h) and dry ether added to give the imidazolidine hydrobromide (5.4 g, 59%), m.p. 169—170 °C (from propan-2-ol) (lit.,[25] 153—160 °C); *m/e* 113; $\nu_{max.}$(KBr) 3 420, 1 690, and 1 602 cm^{-1}. Treatment with sodium methoxide, as above, gave the *free base* as an oil; $\delta_H(CDCl_3)$ 4.44 (1 H, s, NH), 3.22 (4 H, s, 2 × NCH_2), and 2.79 (6 H, s, 2 × NMe).

2-*Acetylimino*-1,3-*dimethylimidazolidine* (**12**).—A solution of acetyl chloride (5.9 ml, 0.083 mol) in chloroform (40 ml) was added dropwise to a solution of 2-imino-1,3-dimethylimidazolidine [from the hydrobromide (19.4 g, 0.1 mol) and sodium methoxide] in chloroform (90 ml). The temperature was kept below 25 °C during the addition and the resulting solution refluxed (1 h). After standing overnight, the solution was filtered (to remove the imine hydrochloride), evaporated, and the residue extracted twice with boiling butanone. Evaporation gave a solid residue of amide hydrochloride (6.2 g, 39%) which was dissolved in methanol and passed through an Amerlite IRA 400 (MeO^-) ion-exchange column to give the *amide*, m.p. 51—52 °C (from diethyl ether–light petroleum); *m/e* 155; $\nu_{max.}$ ($CHCl_3$) 1 595 and 1 545 cm^{-1}; $\delta_H(CDCl_3)$ 3.55 (4 H, s, NCH_2CH_2N), 2.88 (6 H, s, 2 × NMe), 2.12 (3 H, s, COMe); $\delta_C(CDCl_3)$ 174.6 (C=O), 162.3 (C=N), 46.1 (CH_2CH_2), 32.0 (NMe), 25.0 (C-CH_3). Both the salt and the base were too hygroscopic for microanalysis. This compound has been investigated by Kessler and Leibfritz,[26] but its preparation and characterisation were not reported.

2-*Amino*-1-*methyl*-2-*imidazoline Hydrobromide* (**15**).—A solution of cyanogen bromide (25.5 g, 0.25 mol) in methanol (50 ml) was added dropwise to a stirred, ice-cooled solution of *N*-methylethylenediamine (22 ml, 0.25 mol) in methanol (20 ml). The temperature was held below 20 °C until addition was complete and then the solution was refluxed (0.5 h). Evaporation of the solvent gave the imidazoline hydrobromide (38.2 g, 85%), m.p. 233–234 °C (from ethanol) (lit.,[27] 216—217 °C) (Found: C, 26.6; H, 5.7; N, 23.3. Calc. for $C_4H_{10}BrN_3$: C, 26.7; H, 5.7; N, 23.3%); $\nu_{max.}$(KBr) 3 140, 1 675, 1 605, and 1 597 cm^{-1}; δ_H([$^2H_6$]DMSO) 8.05 (3 H, s, 3 × NH), 3.67 (4 H, s, 2 × NCH_2), 3.02 (3 H, s, NMe).

1,2,3,5-*Tetrahydroimidazo*[1,2-a]*pyrimidin*-7(6H)-*one* (**17**).—This compound was prepared from 2-amino-2-imidazoline and ethyl acrylate by the method of Freeman *et al.*[7] (54%), m.p. 231—233 °C (from ethanol–ether) (lit.,[7] 234—235 °C); $\nu_{max.}$ ($CHCl_3$) 1 659, 1 593, and 1 574 cm^{-1}. The tosylate salt of 2-amino-2-imidazoline was prepared from ethylene diamine, toluene-*p*-sulphonic acid, and dimethylcyanamide by the method of

Adcock *et al.*[28] and the free base (**13**) was liberated using Amberlite IRA 400 (MeO^-) with methanol as solvent.

1,2,3,4,6,7-*Hexahydropyrimido*[1,2-a]*pyrimidin*-8-*one* (**18**).—Ethyl acrylate (27.0 ml, 0.27 mol) was added to a solution of 2-iminohexahydropyrimidine [from the tosylate[28] (60.0 g, 0.22 mol) *via* ion exchange] in ethanol (200 ml). An exothermic reaction occurred and the product was stirred overnight at room temperature. The solvent was evaporated to give the *pyrimidopyrimidone* (25.5 g, 75%), m.p. 264—265 °C (from ethanol–ether) (Found: C, 50.6; H, 7.5; N, 25.2. $C_7H_{11}N_3O.0.75$ H_2O requires C 50.5; H, 7.5; N, 25.2%); *m/e* 153; $\nu_{max.}$(Nujol) 3 070, 1 630, and 1 575 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.75 (1 H, s, NH), 3.5—3.0 (6 H, m, 3 × NCH_2), 2.28 (2 H, t, $COCH_2$), and 1.87 [2 H, quintet C(3)H_2].

1-*Methyl*-1,2,3,5-*tetrahydroimidazo*[1,2-a]*pyrimidin*-7(6H)-*one* (**19**).—To a solution of 2-amino-1-methyl-2-imidazoline [from the hydrobromide (18.0 g, 0.1 mol) and sodium ethoxide] in ethanol (40 ml), ethyl acrylate (12 ml, 0.11 mol) was added carefully with cooling. The mixture was stirred overnight and the solvent evaporated to give the *imidazopyrimidone* (14.5 g, 95%), m.p. 108—110 °C (from butanone) (Found: C, 55.3; H, 7.4; N, 27.6. $C_7H_{11}N_3O$ requires C, 54.9; H, 7.3; N, 27.4%); $\nu_{max.}$(Nujol) 1 659 and 1 549 cm^{-1}; δ_H($CDCl_3$) 3.55 (4 H, m, 2 × NCH_2), 3.36 [2 H, t, C(2)H_2], 3.00 (3 H, s, NMe), and 2.62 (2 H, t, $COCH_2$).

9-*Methyl*-3,4,6,7,8,9-*hexahydropyrimido*[1,2-a]*pyrimidin*-2-*one Hydriodide* (**20**).—Ethyl acrylate (10.8 ml, 0.11 mol) was added to a solution of 2-imino-1-methylhexahydropyrimidine [from the hydrobromide[24] (19.4 g, 0.1 mol) and sodium methoxide] in ethanol (60 ml) and stirred overnight. The ethanol was evaporated, 57% hydriodic acid (13 ml) added, and the excess removed by azeotropic co-distillation with toluene to give the *pyrimidopyrimidone hydriodide* (7.2 g, 24%), m.p. 172—174 °C (from ethanol–diethyl ether) (Found: C, 32.7; H, 4.8; N, 14.2. $C_8H_{14}IN_3O$ requires C, 32.6; H, 4.8; N, 14.2%). A methanolic solution, by ion exchange, gave the free base as a rapidly deliquescent solid, which was evaporated onto a cold finger *in vacuo* (0.03 Torr, 135 °C bath temperature), m.p. 111—113 °C; $\nu_{max.}$ ($CHCl_3$) 1 638, 1 563, and 1 510 cm^{-1}; δ_H($CDCl_3$) 3.29—3.48 (6 H, m, 3 × CH_2N), 3.13 (3 H, s, NMe), 2.53 (2 H, t, CH_2CO), and 2.10 [2 H, quintet, C(7)H_2].

8-*Methyl*-2,3,5,6-*tetrahydroimidazo*[1,2-a]*pyrimidin*-7(8H)-*one* [**22**).—*Method* (1). A solution of 1,2,3,5-tetrahydroimidazo[1,2-*a*]pyrimidin-7(6*H*)-one[7] (8.9 g) in iodomethane (40 ml) was refluxed overnight. Excess of iodomethane was evaporated to give the *imidazopyrimidone hydriodide* (14.5 g, 80%), m.p. 209 °C (from ethanol–ether) (Found: C, 29.9; H, 4.3; I, 45.1; N, 15.0. $C_7H_{12}IN_3O$ requires C, 29.9; H, 4.3; I, 45.2; N, 14.9%); $\nu_{max.}$(KBr) 3 110, 1 725, 1 630, and 1 600 cm^{-1}; δ_H(CD_3OD) 3.96 (4 H, s, 2 × NCH_2), 3.68 [2 H, t, C(5)H_2], 3.22 (3 H, s, NMe), and 3.00 (2 H, t, $COCH_2$). A methanol solution was passed through an Amberlite IRA 400 (MeO^-) column to give the *free base* (85%), m.p. 67—69 °C (from light petroleum, b.p. 80—100 °C) (Found: C, 54.5; H, 7.4; N, 27.3. $C_7H_{11}N_3O$ requires C, 54.9; H, 7.3; N, 27.4%); $\nu_{max.}$(Nujol) 1 683 and 1 632 cm^{-1}; δ_H($CDCl_3$) 3.65 [2 H, t, C(2)H_2], 3.35 [2 H, t, C(3)H_2], 3.27 (3 H, s, NMe), 3.15 [2 H, t, C(5)H_2], and 2.87 (2 H, t, $COCH_2$).

Method (2). A solution of ethyl acrylate (1.2 ml, 11 mmol) in ethanol (5 ml) was added to a cold (< 5 °C) solution of 2-methylamino-2-imidazoline [from the hydriodide[29] (2.27 g, 10 mmol) *via* ion exchange] in ethanol (15 ml) and refrigerated (72 h). The solvent was evaporated *in vacuo* with minimum heat to give an oil that was extracted with boiling light petroleum (b.p. 80—100 °C) to yield the *imidazopyrimidone* (0.35 g, 23%), m.p. 63—65 °C, identical (i.r.) with the product from method (1). The insoluble residue (0.94 g, 61%), m.p. 75—80 °C, was identical (i.r.) with compound (**25**) below.

Similarly, from 1,2,3,4,6,7-hexahydropyrimido[1,2-*a*]pyrimidin-8-one (28.8 g) was obtained 1-*methyl*-1,3,4,6,7,8-*hexahydropyrimido*[1,2-a]*pyrimidin*-2-*one hydriodide* (**23**) (44.5 g, 80%), m.p. 186 °C (from ethanol) (Found: C, 32.4; H, 4.8; I, 43.0; N, 14.2. $C_8H_{14}IN_3O$ requires C, 32.6; H, 4.9; I, 43.0; N, 14.2%); $\nu_{max.}$(KBr) 3 190, 1 725, 1 645, and 1 570 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.88 (1 H, s, NH), 3.82—3.22 (6 H, m, 3 × NCH_2), 3.08 (3 H, s, NMe), 2.82 (2 H, t, $COCH_2$), and 1.97 [2 H, quintet, C(7)H_2]. Ion exchange gave the *free base*, m.p. 65 °C (from light petroleum, b.p. 60—80 °C) (Found: C, 57.1; H, 7.9; N, 25.2. $C_8H_{13}N_3O$ requires C, 57.5; H, 7.9; N, 25.1%); $\nu_{max.}$(Nujol) 1 682 and 1 636 cm^{-1}; δ_H($CDCl_3$) 3.6—3.00 (6 H, m, 3 × NCH_2), 3.15 (3 H, s, NMe), 2.62 (2 H, t, $COCH_2$), 1.85 [2 H, quintet, and C(7)H_2].

2,3,7,8-*Tetrahydroimidazo*[1,2-a]*pyrimidin*-5(6H)-*one* (**24**) *and its Salts.*—*Method* (1). A solution of *N*-(2-imidazolin-2-yl)-β-alanine (**26**) (1.6 g, 10 mmol) in concentrated hydrochloric acid (10 ml) was refluxed (3.5 h). The solvent was evaporated and the residue azeotroped with toluene until it solidified to give the *imidazopyrimidone hydrochloride* (0.64 g, 37%), m.p. 255—256 °C (from ethanol–ether) (Found: C, 41.4; H, 5.7; Cl, 19.9; N, 24.3. $C_6H_{10}ClNO_3$ requires C, 41.0; H, 5.8; Cl, 20.2; N, 23.9%). The *hydrobromide* was similarly prepared (51%), m.p. 234—235 °C (from ethanol) (Found: C, 33.2; H, 4.6; Br, 36.2, N, 19.2. $C_6H_{10}BrN_3O$ requires C, 32.8; H, 4.6; Br, 36.3; N, 19.1%).

Method (2). A solution of sodium hydroxide (7.0 g, 0.16 mol) and 2-methylthio-2-imidazolinium iodide[29] (40.0 g, 0.16 mol) in water (170 ml) was mixed with a solution of β-alanine (14.6 g, 0.16 mol) in water (70 ml) and left to stand until the evolution of methanethiol had ceased (1 week). The solution was saturated with hydrogen chloride with stirring and cooling, the supernatant liquid decanted off, the residue washed with hydrochloric acid, and the total acid solution refluxed (3 h). The solvent was evaporated, the residue dissolved in a minimum amount of methanol, filtered (to remove residual sodium chloride), and the methanol evaporated to give the *imidazopyrimidone hydriodide* (31.1 g, 71%), m.p. 174—176 °C (from ethanol) (Found: C, 27.2; H, 3.8; I, 47.4; N, 15.9. $C_6H_{10}IN_3O$ requires C, 27.0, H, 3.8; I, 47.5; N, 15.7%); $\nu_{max.}$(Nujol) 3 300—3 000, 1 724, 1 695, and 1 542 cm^{-1}; δ_H(CD_3OD) 3.85 (6 H, m, 3 × NCH_2) and 2.84 (2 H, t, $COCH_2$). Ion-exchange gave the free base, m.p. 137—139 °C (from ethanol) (lit.,[7] 139—140 °C).

Method (3). A solution of *N*-(2-imidazolin-2-yl)-β-alanine[30] (0.8 g, 5 mmol), toluene-*p*-sulphonic acid (1.1 g, 5.5 mmol), and dicyclohexylcarbodi-imide (1.1 g, 5.5 mmol) in ethanol (200 ml) was stirred on an ice-bath (5 h) and refrigerated overnight to give the *imidazopyrimidone tosylate* (from water–ethanol) (0.46 g, 26%), m.p. 264—265 °C (decomposed) (Found: C, 50.2; H, 5.6; N, 13.5; S, 10.4. $C_{13}H_{17}N_3O_4S$ requires C, 50.1; H, 5.5; N, 13.5; S, 10.3%); $\nu_{max.}$(KBr) 3 150, 1 725, and 1 562 cm^{-1}.

8-*Methyl*-2,3,7,8-*tetrahydroimidazo*[1,2-a]*pyrimidin*-5(6H)-*one* (**25**).—*Method* (1). A solution of 5-imino-1-methyl-1,2,3,5,6,7-hexahydroimidazo[1,2-*a*]pyrimidinium iodide (38.8 g) in water (60 ml) was evaporated on a boiling water bath under vacuum to give the *imidazopyrimidone hydriodide* (34.4 g, 88%), m.p. 235—237 °C (from ethanol) (Found: C, 29.7; H, 4.2; I, 45.1; N, 14.8. $C_7H_{12}IN_3O$ requires C, 29.9; H, 4.3; I, 45.1; N, 15.1%); $\nu_{max.}$(Nujol) 3 100, 1 731, 1 703, and 1 532 cm^{-1}; δ_H ([$^2H_6$]DMSO) 5.19 (1 H, s, NH), 3.80 (4 H, m, 2 × NCH_2), 3.65 [2 H, t, C(7)H_2], 3.11 (3 H, s, NMe), and 2.75 (2 H, t, $COCH_2$). Passage through an ion-exchange column gave the *free base*,

m.p. 100—102 °C (from butanone) (Found: C, 55.4; H, 7.3; N, 27.4. $C_7H_{11}N_3O$ requires C, 54.9; H, 7.3; N, 27.4%); $\delta_H(CDCl_3)$ 3.79 (4 H, s, 2 × NCH_2), 3.20 [2 H, t, C(7)H_2], 3.01 (3 H, s, NMe), and 2.66 (2 H, t, $COCH_2$).

Method (2). A solution of 2-methylamino-2-imidazoline [from the hydriodide[29] (2.27 g) *via* ion exchange] in ethyl acrylate (20 ml) was refluxed (30 min) and excess of ethyl acrylate evaporated to give the imidazopyrimidone (0.8 g, 52%), m.p. 100—102 °C, identical (mixed m.p., i.r.) with the sample prepared above.

N-(1-*Methyl*-2-*imidazolin*-2-*yl*)-β-*alanine* (**27**).—A solution of β-alanine (17.8 g, 0.2 mol) in water (100 ml) was added to a solution of 1-methyl-2-methylthio-2-imidazolinium iodide[31] (51.4 g, 0.2 mol) and sodium hydroxide (8 g, 0.2 mol) in water (100 ml) and the mixture set aside until the evolution of methanethiol had ceased (50 h). The solution was diluted with water (1.3 l) and passed through a mixed bed ion-exchange column [200 ml Amberlite IRA 400 (OH) and 200 ml Amberlite RC50 (H)] at 12—14 ml min^{-1}. The column was washed with water (800 ml) and the combined filtrates evaporated to give the *imidazoline* (12.4 g, 36%), m.p. 221—222 °C (from ethanol), *m/e* 171; $\nu_{max.}$(KBr) 3 045, 2 950, 1 665, 1 595, and 1 570 cm^{-1}; $\delta_H(CD_3OD)$ 3.75 (2 H, t, NCH_2), 3.67 (4 H, s, 2 × NCH_2), 2.92 (3 H, s, NMe), and 2.43 (2 H, t, CH_2CO_2H). The mother liquor was evaporated to give 1-methylimidazolidin-2-one, m.p. 115—116 °C (from ethanol–ether) (lit.,[32] 115—116 °C).

1-*Methyl*-1,2,3,7-*tetrahydroimidazo*[1,2-a]*pyrimid*-5(6H)-*one* (**28**).—A solution of *N*-(1-methyl-2-imidazolin-2-yl)-β-alanine (12.4 g) in concentrated hydrobromic acid (100 ml) was refluxed (3.5 h). The solvent was evaporated and the residue azeotroped with toluene to give the *imidazopyrimidone hydrobromide* (13.4 g, 79%), m.p. 198—199 °C (from ethanol) (Found: C, 35.8; H, 5.1; Br, 34.6; N, 17.9. $C_7H_{12}BrN_3O$ requires: C, 35.9; H, 5.1; Br, 34.2; N, 17.9%); $\nu_{max.}$(Nujol) 3 100—2 800, 1 730, 1 701, and 1 537 cm^{-1}; $\delta_H(CD_3OD)$ 4.14 (4 H, m, 2 × NCH_2), 3.93 (2 H, t, NCH_2), 3.30 (3 H, s, NMe), and 2.94 (2 H, t, $COCH_2$). Ion exchange gave the *free base* as an oil; $\nu_{max.}$(neat) 1 680 cm^{-1}; $\delta_H(CDCl_3)$ 3.80 (6 H, m, 3 × NCH_2), 3.00 (3 H, s, NMe), and 2.52 (2 H, t, $COCH_2$).

5-*Imino*-8-*methyl*-2,3,5,6,7,8-*hexahydroimidazo*[1,2-a]*pyrimidinium Iodide* (**30**).—A solution of 2-methylthio-2-imidazolinium iodide[29] (104.4 g, 0.43 mol) and 3-methylaminopropionitrile (40 ml, 0.43 mol) in ethanol (120 ml) was refluxed (1.5 h) and refrigerated overnight. The precipitate was collected to give the *imidazopyrimidinium iodide* (32.3 g, 27%), m.p. 219—221 °C (from methanol) (Found: C, 29.8; H, 4.9; N, 19.8. $C_7H_{13}IN_4$ requires C, 30.0; H, 4.7; N, 20.0%); $\nu_{max.}$(Nujol) 3 200—3 050, 1 684, 1 655, and 1 548 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 5.83 (2 H, s, 2 × NH), 3.85 (4 H, s, 2 × NCH_2), 3.50 [2 H, t, C(7)H_2], 3.05 (3 H, s, NMe), and 2.90 [2 H, t, C(6)H_2].

4-(2-*Imidazolin*-2-*ylamino*)*butyric Acid* (**31**).—This compound was prepared by the method of McKay and Hatton[30] (91%), m.p. 221—223 °C (from methanol) (lit.,[30] 224—225 °C); $\nu_{max.}$(KBr) 3 430, 3 230, 1 700, and 1 550 cm^{-1}; $\delta_H(D_2O)$ 3.70 (4 H, s, 2 × CH_2N), 3.21 (2 H, t, CH_2CO), and 2.5—1.6 (4 H, m, 2 × CH_2).

1-(2-*Imidazolin*-2-*yl*)*pyrrolidin*-2-*one* (**32**).—This compound was prepared as described by Freeman *et al.*,[7] (88%), m.p. 97—99 °C (lit.,[7] about 105 °C). A sample of this material exposed to air absorbed water and carbon dioxide and was then insoluble in chloroform. The bulk of the sample was converted into its picrate, m.p. 194—195 °C (from methanol) (lit.,[7] 192—193 °C); $\nu_{max.}$(KBr) 3 380, 1 738, and 1 622 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 9.35 (2 H, s, 2 × NH), 8.60 (2 H, s, 2 × ArH), 3.75 (2 H, t, $CONCH_2$), 3.75 (4 H, s, NCH_2CH_2N), 2.60 (2 H, t, CH_2CO), and 2.15 (2 H, m, $CH_2CH_2CH_2$). The free base was recovered as required by shaking the picrate with an ice-cold, carbon dioxide (solid CO_2)-saturated mixture of water, di-isopropylethylamine, and dichloromethane; the aqueous phase was separated, freeze dried, and the residue sublimed (0.05 Torr, 90 °C bath temperature) to yield the crystalline base which was stored under argon; $\delta_C(CDCl_3)$ 175.7 (C=O), 156.95 (C=N), 47.8 (NCH_2CH_2N), 46.8 ($CONCH_2$), 32.3 (CH_2CO), and 17.9 ($CH_2CH_2CH_2$).

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