# Nucleophilic Substitution in Quaternary Salts of *NN'*-Linked Biazoles and Related Systems.[1]

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Some reactions of dicationic and monocationic *N,N'*-linked biazoles and of quaternized 1-(*N*-azolyl)pyridinium ions with nucleophiles have been studied. Although the pyrrolyl nucleus has been found to be a poor leaving group in these reactions, in other cases nucleophilic attack readily takes place at an azolyl carbon atom, with subsequent elimination of the *N*-substituent. The 1-methyl-3-(1-methyl-1,2,4-triazol-4-ylio)benzimidazolium dication (**1**) reacted at room temperature with ammonium, diethylamine, methoxide, hydroxide, and cyanide ions, and with sodium borohydride, giving in all cases the corresponding 2-substituted benzimidazoles in good yield. In the case of the 2,4,6-trimethyl-1-(2-methylpyrazol-1-io)pyridinium dication (**6**), the reaction with cyanide ion afforded, regioselectively, 5-cyano-1-methylpyrazole, with no trace of the isomeric 3-cyano-1-methylpyrazole.

The synthesis of the cations and dications from *N*-aminoazoles was easily performed. The reaction of 1-aminobenzimidazole with dehydroacetic acid in aqueous hydrochloric acid gave not only the expected 1-benzimidazol-1-yl-2,6-dimethylpyridin-4(1*H*)-one (**9**), but also 3-acetyl-1-benzimidazol-1-yl-4-hydroxy-6-methylpyridin-2(1*H*)-one (**11**). In pyridine, a pyran-2,4-dione intermediate (**10**), isomeric to (**11**), was also isolated. The quaternization reactions were easily performed, but high temperatures caused cleavage of the N–N bond.

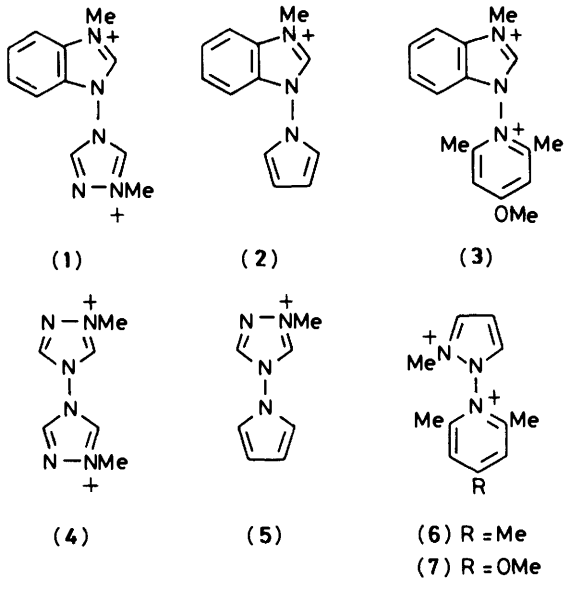
The activation of heterocycles towards nucleophilic substitution by quaternization with a *N*-substituent which could act as a leaving group has found wide application in the pyridine series, with *N*-alkoxypyridinium ions as substrates, and cyanide ion,[2] Grignard reagents,[3] or methylene active compounds,[4] as the nucleophiles. The initial attack of the nucleophile at the 2- or 4-position of the pyridinium cation is, in general, followed by the rearomatization of the ring by loss of alcohol. The extension of this strategy to 1-pyridinio-4-pyridone cations, made recently by Katritzky's group,[5] allows for the same reactions to be carried out with a high degree of regioselectivity at position 4, especially when the pyridone ring has additional substituents at the 2- and 6-positions.

In the azole series, to date very few studies on the reaction of *N*-alkoxy- or *N*-heterocyclic bonded azolium ions with nucleophiles have been carried out. This is not surprising if one considers the facile ring opening of the quaternary salts of azoles in basic media.[6] To the best of our knowledge, only the reactions of 1-methoxy-3-methylbenzimidazolium iodide with a variety of nucleophiles have been investigated to any extent, giving in all cases good yields of the corresponding 1-methyl-2-substituted benzimidazoles.[7] No examples are known of similar reactions with azolium ions *NN'*-linked to other heterocycles (neutral or charged molecules) which could act as the leaving group. One probable exception, however, is the reported cleavage of 3,3'-dimethyl-1,1'-bibenzotriazolium methylsulphate with lithium aluminium hydride to 1-methylbenzotriazole (2 equiv.). The ease of this reaction contrasts with the stability of the unalkylated compound towards the same reagent.[8]

We report in this paper the synthesis of the cations and dications (**1**)—(**7**), and their behaviour in basic media or in the presence of cyanide ion and other nucleophiles.

## Results and Discussion

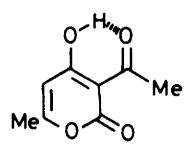
*Synthesis.*—Compounds (**1**)—(**7**) were prepared in a few steps from the corresponding *N*-aminoazoles, *i.e.*, 1-aminobenzimidazole,[9] 1-aminopyrazole,[10] or the commercially available 4-amino-1,2,4-triazole. Cyclization of the 1,2,4-triazol-4-yl and pyrrol-1-yl rings can be conveniently performed by *NN*-dimethylformamide azine,[9,11] and 2,5-diethoxytetrahydrofuran,[9,12] respectively. For the cyclization of the 2,6-dimethyl-4-pyridone ring [compounds (**3**) and (**7**)] we followed the method described by Katritzky for 2,6-dimethyl-1-(1,2,4-triazol-4-yl)-4-pyridone,[13] using dehydroacetic acid (**8**) and the corresponding 1-aminoazole. Although no problems were encountered under standard experimental conditions (reflux in pyridine) in the case of pyrazole, the reaction failed to give the expected compound (**9**) when applied to 1-aminobenzimidazole, the intermediate (**10**) being isolated instead.




(**1**) (**2**) (**3**)

(**4**) (**5**) (**6**) R = Me
(**7**) R = OMe

Structure (**10**) is supported by analytical data and by i.r. and $^1$H n.m.r. spectra. Proton signals for methyl groups



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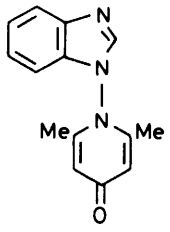

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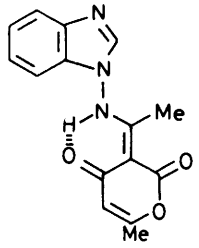

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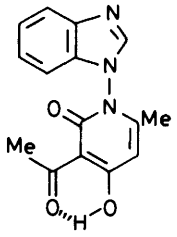


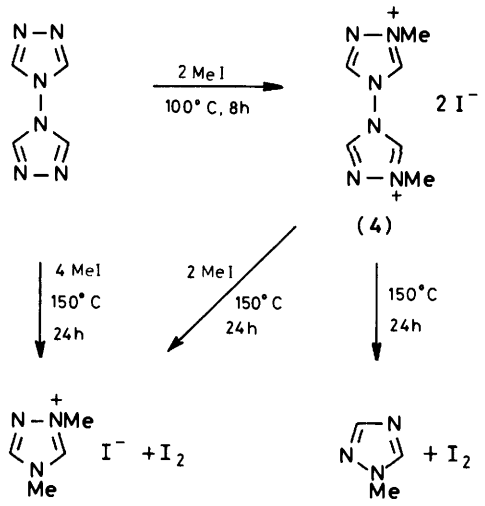
(11)

appear at 2.25 and 2.49 p.p.m. Moreover, other structures similar to (**10**) have been previously reported in reactions of dehydroacetic acid with amine derivatives.[13,14] These data alone, however, do not eliminate the alternative structure (**11**) for the intermediate; this structure was ruled out on the basis of chemical evidence. The treatment of the compound with hot aqueous hydrochloric acid yielded quantitatively the desired 4-pyridone (**9**) as the hydrochloride. A similar acid-catalysed decarboxylation could not be possible from (**11**). This behaviour has also been observed in analogues of (**10**).[13] Curiously, if the reaction of 1-aminobenzimidazole with dehydroacetic acid is carried out directly in concentrated hydrochloric acid, the expected hydrochloride of (**9**) is readily obtained, together with an isomer of (**10**), whose structure could actually be (**11**). Although there is no precedent for a reaction of dehydroacetic acid with amine derivatives to yield a 2-pyridone like (**11**), the i.r. and $^1$H n.m.r. spectra of the compound (proton signals of the methyl groups at 2.04 and 2.56 p.p.m.), as well as its inertness to decarboxylate under the acidic conditions of the reaction, are fully consistent with this assignment.

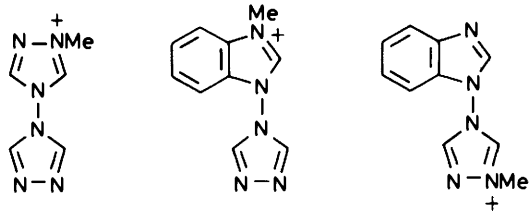
The quaternization of the resulting bicyclic compounds to the structures (**1**)—(**7**) was performed with either methyl iodide or methyl sulphate. The counterion was changed in some instances to tetrafluoroborate to facilitate crystallization. In the case of the pyrrolyl structures (**2**) and (**5**), ion-exchange was not possible from the iodides, and attempts to isolate the methylsulphates failed too, yielding instead open-chain products. Since most of the cations and dications (**1**)—(**7**) were found to be sensitive to moisture or protic solvents (see below), care was taken during the methylations to avoid, or keep to a minimum, the presence of such solvents.

Another limitation to the quaternization reaction was the thermal instability of the dications. For example, 4,4′-bi-1,2,4-triazole, which is a stable compound at temperatures below 250 °C, was easily quaternized to (**4**) at 100 °C with methyl iodide, but gave only the cleaved product, 1,4-dimethyl-1,2,4-triazolium iodide, at 150 °C. If the dication (**4**) was heated to 150 °C, it decomposed to 1-methyl-1,2,4-triazole, or to 1,4-dimethyl-1,2,4-triazolium iodide in the presence of methyl iodide (Scheme 1). Similar results were obtained with dimethyl sulphate as the alkylating agent.

Some attempts to isolate the monocationic species (**12**), (**13**), and (**14**), by carefully controlling the stoicheiometry of the




**Scheme 1.**



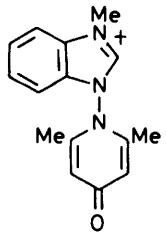
(12) (13) (14)

reagents were unsuccessful, and in all instances mixtures of both the dication and the starting dimer were isolated.

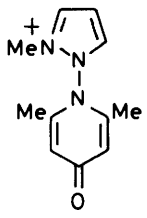
In the case of 1-(1,2,4-triazol-4-yl)benzimidazole, a mixture of the dication (**1**), starting material, and small amounts of both monocations (**13**) and (**14**) was detected by $^1$H n.m.r., when the starting compound was allowed to react with a small amount of dimethyl sulphate in anhydrous hexadeuteriated dimethyl sulphoxide. Assuming that a Brønsted correlation of the rate of quaternization *vs.* the basicity operates in the series,[15] one could expect the benzimidazolyl nitrogen atom to be the most reactive, if we take into account the relative basicities of the parent rings, *i.e.*, 1-methylbenzimidazole ($pK_a$ = 5.50)[16] and 4-methyl-1,2,4-triazole ($pK_a$ = 3.40),[17] despite the fact that both nitrogen atoms of the triazolyl moiety yield the same cation. Indeed, a determination of the first $pK_a$ of 1-(1,2,4-triazol-4-yl)benzimidazole by potentiometry gave a value of 1.34 ± 0.06 (at 21 °C), and a similar value (1.37 ± 0.02) was obtained spectrophotometrically. Since we found no changes in the u.v. spectra of the model compound 4-phenyl-1,2,4-triazole[11] in neutral or acidic media, we can confidently deduce that protonation takes place at the benzimidazolyl ring, the low value of the $pK_a$ being due mainly to the strong attracting character of the other heterocycle. On the other hand, a theoretical prediction, based on MNDO calculations,[18] shows both a higher charge density and a better contribution of the orbitals of benzimidazole towards methylation. Experimentally, both monocations are minority species in the mixture, and the dication is present from the early steps of the reaction. We must therefore conclude that the rates of diquaternization of the monocations (**13**) and (**14**) do not appreciably differ from those of their formation, so that any attempt to estimate the relative rates of monoquaternization becomes difficult, and precludes the isolation of one or both monocationic species.

*Reactivity.*—The methoxy group at the pyridine ring in

compounds (3) and (7) was found to be the most reactive position of these compounds towards nucleophilic attack, yielding the demethylated pyridones (15) and (16), respectively, by simply adding water to the dications. The resulting monocations were quite stable in water, showing the poor activity of the pyridine ring as a leaving group, so that further investigations into the reactions of these species with other nucleophiles were not pursued.



(15)



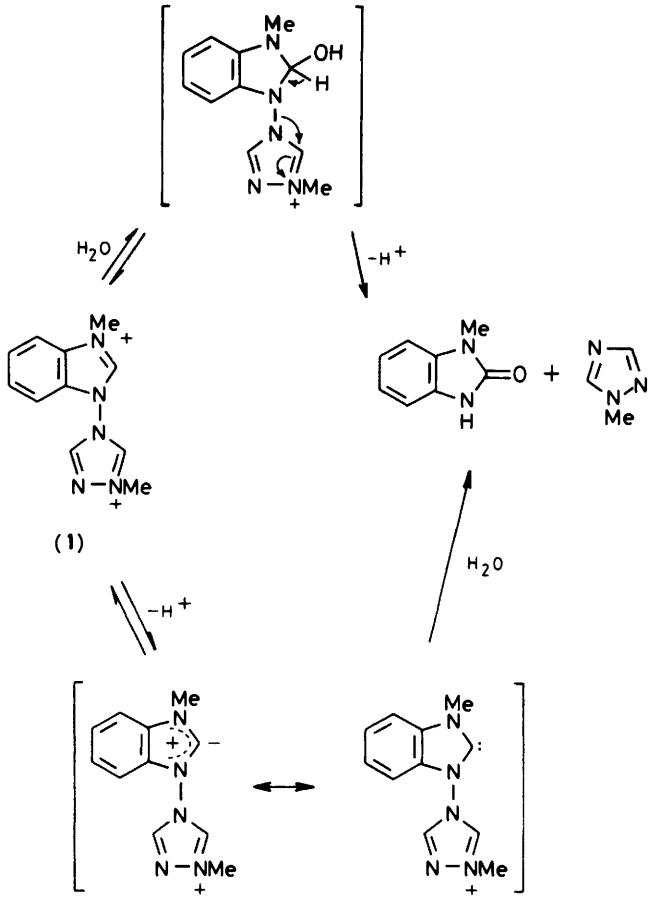
(16)

In contrast, the triazolylbenzimidazole dication (1) was readily cleaved with water at room temperature, giving quantitatively equimolecular amounts of 1-methylbenzimidazol-2-one and 1-methyl-1,2,4-triazole. This product composition shows that the solvent has reacted exclusively at position 2 of the benzimidazolyl ring.

Two mechanistic pathways can be envisaged for this reaction. The process could either be initiated by the attack of water on the benzimidazole, followed by deprotonation and N–N bond cleavage of the resulting intermediate or, alternatively, an initial deprotonation could give a zwitterion intermediate whose electrophilic carbene-type resonance hybrid would react with the solvent to yield the final products (Scheme 2). This last mechanism is well documented from the pioneering work of Breslow on the thiamine action,[19] and has been proposed for the reactions of 1-methoxy-3-methylbenzimidazolium iodide with some nucleophiles.[7]

Although we have not investigated in detail the mechanistic aspects of the reaction, the following facts must be emphasized from a $^1$H n.m.r. study. (i) The reaction is notably accelerated in the presence of dimethyl sulphoxide. A kinetic run made in $[(CD_3)_2SO]$–water (1:1) showed typical first-order kinetics, with a rate constant of $7.78 \times 10^{-4}$ s$^{-1}$. A further experiment in a mixture with deuteriated water gave a value of $4.75 \times 10^{-4}$ s$^{-1}$. The moderate kinetic isotope effect (1.64) is compatible with the addition–elimination mechanism. (ii) Very rapid H/D exchange was observed at position 5 of the triazolium ring, and a somewhat slower process at the 2 position of the benzimidazolium ring. Both processes were, however, faster than the reaction with the nucleophile. If a zwitterion–carbene mechanism operates, the rate of the reaction of the intermediate with the solvent should be greater than the rate of its formation. (iii) Although the H/D exchange is faster on the triazolium ring than on the benzimidazolium ring, evidence for products resulting from solvent attack on the triazole was not detected in the spectrum. All these facts are in agreement with the addition–elimination mechanism as the most probable for the reaction.

Some basic reagents were also tested against compound (1). In all cases, the triazolyl ring was degraded in the basic medium to unidentified open-chain products, but the reaction indeed took place readily at the benzimidazole ring, yielding the corresponding 2-substituted benzimidazoles. Thus, the action of diethylamine in dichloromethane gave 2-(*N*,*N*-diethylamino)-1-methylbenzimidazole, and in concentrated ammonium hydroxide solution a mixture of 2-amino-1-methylbenzimidazole and bis(1-methylbenzimidazol-2-yl)amine was



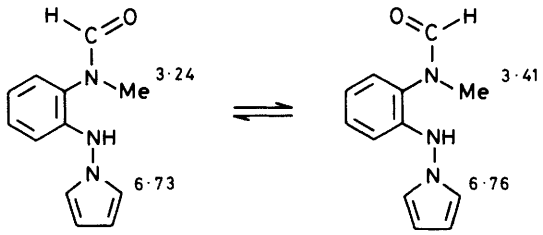
Scheme 2.

formed. The solvolytic process predominated, however, if the reaction with diethylamine was performed in water, the corresponding 1-methylbenzimidazol-2-one being the only isolated product. Similarly, methanolic sodium methoxide reacted with (1) giving almost quantitatively 2-methoxy-1-methylbenzimidazole. This proves again that the most reactive centre of the molecule is the position 2 of the benzimidazolyl ring. The high yield of this reaction suggests that the ring-opening of the triazolyl moiety should take place *after* the N–N bond had been broken. Indeed, a sample of 1-methyl-1,2,4-triazole rapidly decomposed in methanolic solution when 1.5 equiv. of sodium methoxide were added.

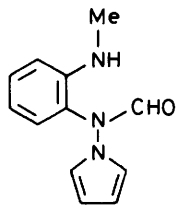
The reaction of the dication (1) with sodium borohydride in methanol gave a mixture of products from both the attack of the hydride and the solvent, *i.e.*, 1-methoxybenzimidazole and 2-methoxy-1-methylbenzimidazole, respectively. Finally, if compound (1) was dissolved in saturated aqueous sodium cyanide, 2-cyano-1-methylbenzimidazole was formed in high yield, together with a small amount of 1-methylbenzimidazol-2-one. The formation of benzimidazolone can be avoided if the reaction is carried out in a two-phase system, compound (1) being shaken in a mixture of chloroform and saturated aqueous sodium cyanide. Under these conditions, the yield of 2-cyano-1-methylbenzimidazole is quantitative.

We found that the pyrrolyl ring was a poor leaving group in these reactions. This allowed us, however, to have some insight on the structures derived from the ring-opening of benzimidazolium cations. For example, the action of sodium methoxide on the 1-methyl-3-pyrrol-1-ylbenzimidazolium cation (2) gave a solid compound, identified as the formamide (17) on the basis of its mass and proton n.m.r. spectra. The

alternative isomeric structure (**18**) was discarded because of the following considerations: the n.m.r. spectrum of the compound shows the two conformers around the amide bond, (**17a**) and (**17b**), in a 77:23 ratio. Methyl signals appear as two well separated singlets at 3.24 and 3.41 p.p.m., the former corresponding to the most abundant conformer. On the other hand, the shifts of the α-pyrrolyl protons in the two conformers are little different. For structure (**18**) we could reasonably expect the reverse behaviour: the α-pyrrolyl protons, near to the carbonyl group in one conformer, should appear with a large separation, and the methyl signals close together, at chemical shifts not far from the methyl signal of *N*-methylaniline (2.78 p.p.m.) By comparison with data for *NN*-disubstituted formamides[20] we can assign the most abundant conformer to the *E*-form (**17a**).



(17a) (17b)



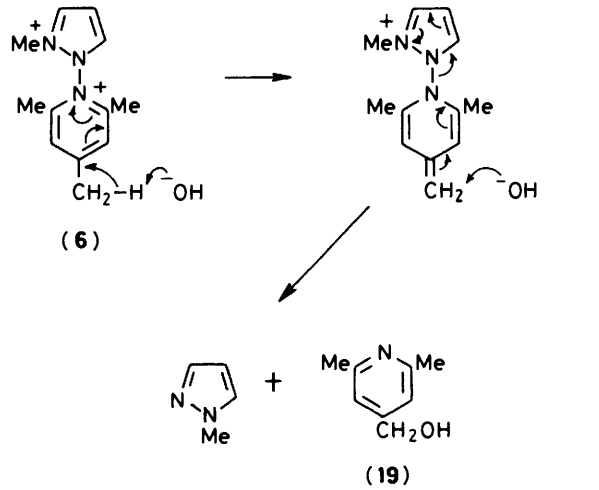
(18)

As expected from the results described above for the dication (**1**), all attempts to isolate triazole derivatives from the reactions of the 1,1′-dimethyl-4,4′-bi-1,2,4-triazolium dication (**4**) were unsuccessful. The reaction of hydroxide or cyanide ions, as well as the reaction with diethylamine, gave in each case open-chain products.

Finally, some reactions of the pyrazolyl dication (**6**) were investigated. In basic media (dilute sodium hydroxide or diethylamine) the main product was 4-hydroxymethyl-2,6-dimethylpyridine (**19**), probably formed by deprotonation of the methyl group at position 4, followed by attack of hydroxide (Scheme 3). There was no trace of the volatile 1-methylpyrazole or any other pyrazolyl-containing product, thus showing that preferential attack at the pyridinium ring had occurred.

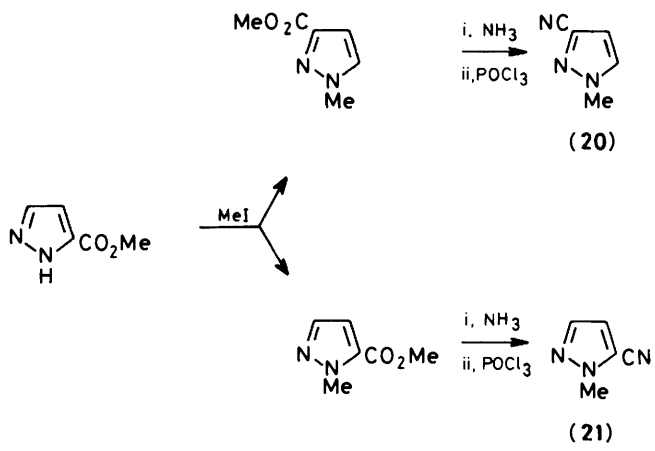
When a related reaction was carried out rapidly at room temperature in water–chloroform with a good nucleophile such as the cyanide anion, the organic layer showed equal amounts of 5-cyano-1-methylpyrazole and collidine, 60% of the starting material being recovered from the aqueous layer. No trace of the isomeric 3-cyano-1-methylpyrazole was found. This highly regioselective reaction of a nucleophile with a pyrazolium cation is unprecedented, and deserves interest for its potential synthetic application, provided that concurrent attack at the *N*-substituent can be avoided. We are actively investigating further reactions of compound (**6**) and other related structures with nucleophiles.

All the C-substituted heterocycles described by cleavage of the *N*,*N*′-bonded quaternary salts of this study were identified by comparison with authentic samples. In the case of 5-cyano-1-methylpyrazole, the compound was identified by comparison with both isomers (**20**) and (**21**), prepared in an unequivocal way from the corresponding carboxamides (Scheme 4).



(6) (19)

Scheme 3.



(20) (21)

Scheme 4.

## Experimental

Melting points are uncorrected. Column chromatography was performed in silica gel (70—230 mesh). All solvents were distilled and dried prior to use. $^1$H N.m.r. spectra were recorded on Perkin-Elmer R-24, Varian XL-200, or Brucker WM 200 SY instruments. I.r. spectra were recorded on a Pye Unicam SP 1100 instrument and mass spectra on a Hewlett-Packard 5930A spectrometer. Ether refers to diethyl ether.

For the potentiometric determination of the acidity constant of 1-(1,2,4-triazol-4-yl)benzimidazole, the techniques described by Albert and Sergeant[21] were followed. The spectrophotometric determination of p$K_a$ values was performed on a Perkin-Elmer 124 spectrophotometer, in sulphuric acid solutions,[22] with the aid of the graphic method of Maroni and Calmon.[23]

The syntheses of 4-(1,2,4-triazol-4-yl)- and 1-pyrrol-1-yl-benzimidazoles have been described elsewhere.[9] 4,4′-Bi-1,2,4-triazole[11] and 4-pyrrol-1-yl-1,2,4-triazole[12] were prepared according to literature methods. Samples of *N*-methylazoles and of 2-hydroxy-, 2-methoxy,[24] 2-amino-, 2-diethylamino-,[25] and 2-cyano-[24] 1-methylbenzimidazoles, as well as 2,4,6-trimethyl- and 4-hydroxymethyl-2,6-dimethyl-[26] pyridines were

purchased if commercially available or prepared according to known procedures.

*1-Methylpyrazol-3- and -5-carbonitriles* (**20**) and (**21**).—A solution of 3-methoxycarbonyl-1-methylpyrazole[27] (3.7 g, 26 mmol) in concentrated aqueous ammonium hydroxide (80 ml) was stirred at room temperature until complete disappearance of the starting material, as monitored by t.l.c. The resulting solution was extracted with chloroform, and the extract washed with water, dried, and evaporated to give 1-methylpyrazole-3-carboxamide (2.8 g, 86%), m.p. 139—141 °C (lit.,[28] 139—140.5 °C). Phosphoryl chloride (2.4 ml) was added dropwise (30 min) to a stirred solution of the crude amide (2.2 g, 18 mmol) in pyridine (40 ml) maintained at −5 °C. The resulting mixture was stirred for a further 2 h at −5 °C, and then poured into ice, acidified to pH *ca.* 3, and extracted with chloroform. The extract was dried and evaporated to yield *1-methylpyrazole-3-carbonitrile* (**20**) (1.7 g, 85%), m.p. (from cyclohexane) 42—44 °C (Found: C, 55.8; H, 5.7; N, 33.8. $C_5H_5N_3$ requires C, 56.05; H, 4.7; N, 39.2%). $\nu_{max.}$(Nujol) 2 245 $cm^{-1}$; $\delta_H(CDCl_3)$ 3.99 (3 H, s, Me), 6.67 (1 H, d, *J* 2.4 Hz, 4-H), and 7.44 (1 H, d, *J* 2.4 Hz, 5-H).

The same sequence from 5-methoxycarbonyl-1-methylpyrazole[27] gave 1-methylpyrazole-5-carboxamide (80%), m.p. 124—125 °C, and *1-methylpyrazole-5-carbonitrile* (**21**) (82%), m.p. (from hexane) 23—26 °C (Found: C, 55.8; H, 4.9; N, 39.2. $C_5H_5N_3$ requires C, 56.05; H, 4.7; N, 39.2%); $\nu_{max.}$(Nujol) 2 240 $cm^{-1}$ (lit.,[29] 2 240 $cm^{-1}$); $\delta_H(CDCl_3)$ 4.07 (3 H, s, Me); 6.80 (1 H, s, *J* 2.1 Hz, 4-H), and 7.56 (1 H, s, *J* 2.1 Hz, 3-H) (lit.,[29] 4.07, 6.75, and 7.50).

*2,4,6-Trimethyl-1-pyrazol-1-ylpyridinium Tetrafluoroborate*.—A mixture of 1-aminopyrazole[10] (0.58 g, 7 mmol) and 2,4,6-trimethylpyrylium tetrafluoroborate[30] (1.3 g, 3.5 mmol) was refluxed for 30 min in anhydrous ethanol (50 ml). The mixture was cooled and the crystals formed were filtered off and dried at 100 °C, (1.06 g, 66%), m.p. 168—170 °C (Found: C, 48.1; H, 5.0; N, 15.05. $C_{11}H_{14}N_3{\cdot}BF_4$ requires C, 48.0; H, 5.1; N, 15.3%); $\nu_{max.}$(KBr) 3 070, 3 040, 1 645, 1 585, 1 535, 1 530, 1 120—1 020, 1 035, and 800 $cm^{-1}$; $\delta_H[(CD_3)_2SO]$ 2.33 (6 H, s, 2- and 6-Me), 2.67 (3 H, s, 4-Me), 6.77 (1 H, t, pyraz. 4-H), 8.02 (2 H, s, 3- and 5-H), 8.02 (1 H, d, pyraz. 3-H), and 8.38 (1 H, d, pyraz. 5-H); *m/z* 183 (3%) and 121 (100%).

*2,6-Dimethyl-1-pyrazol-1-ylpyridin-4(1H)-one*.—Dehydroacetic acid (2.02 g, 12 mmol) and 1-aminopyrazole (1.00 g, 12 mmol) were refluxed for 18 h in pyridine (20 ml). The solution was allowed to cool, and the solid formed was filtered off and recrystallized from methanol–acetone (1.46, 64%), m.p. 234—236 °C (Found: C, 63.4; H, 5.8; N, 22.3. $C_{10}H_{11}N_3O$ requires C, 63.5; H, 5.85; N, 22.2%); $\nu_{max.}$(KBr) 3 100, 1 650, 1 450, 1 370, 1 340, 1 000, 870, and 810 $cm^{-1}$; $\delta_H[(CD_3)_2SO]$ 1.81 (6 H, s, Me), 6.08 (2 H, s, 3- and 5-H), 6.57 (1 H, t, pyraz. 4-H), 7.75 (2 H, d, pyraz. 3-H), and 8.25 (1 H, d, pyraz. 5-H).

*3-(1-Aminobenzimidazol-1-ylethylidene)-6-methylpyran-2,4-dione* (**10**).—A mixture of 1-aminobenzimidazole (1.33 g, 10 mmol) and dehydroacetic acid (1.68 g, 10 mmol) was heated under reflux for 12 h in pyridine (20 ml). Elimination of the solvent gave a brown residue, which was purified by column chromatography with dichloromethane–ethyl acetate (1:1) as eluant. The resulting solid was crystallized in methanol, to yield compound (**10**) (1.18 g, 41%), m.p. 185—186 °C (decomp.) (Found: C, 63.25; H, 4.95; N, 14.7. $C_{15}H_{13}N_3O_3$ requires C, 63.6; H, 4.6; N, 14.85%); $\nu_{max.}$(KBr) 3 105, 1 720, 1 585, 1 540, 1 475, 1 320, 1 225, 1 070, 1 000, and 735 $cm^{-1}$; $\delta_H(CDCl_3)$ 2.25 (3 H, d, *J* 0.7 Hz, 6-Me), 2.49 (3 H, s, ethylidene), 5.91 (1 H, q, *J* 0.7 Hz, 5-H), 7.4 (3 H, m, benzim.), 7.86 (1 H, m, benzim. 4-H), 7.90 (1 H, s, benzim. 2-H), and 16.5 (1 H, br s, NH); *m/z* 283 ($M^+$, 35%) and 43 (100%).

*1-Benzimidazol-1-yl-2,6-dimethylpyridin-4(1H)-one* (**9**).—*Method A*. A solution of the pyran-2,4-dione (**10**) (0.35 g) in 50% aqueous hydrochloric acid was refluxed for 12 h. The solvent was evaporated under reduced pressure and the residue recrystallized in ethanol–ether, giving the hydrochloride of compound (**9**) (0.22 g, 65%), m.p. 240—242 °C (Found: C, 60.9; H, 5.4; N, 14.85. $C_{14}H_{14}ClN_3O$ requires C, 61.0; H, 5.1; N, 15.25%). The free base was obtained quantitatively from an aqueous solution of the salt by neutralisation and extraction with chloroform; it had m.p. 280—282 °C; $\nu_{max.}$(KBr) 3 070, 1 635, 1 570, 1 390, 1 225, 1 130, and 725 $cm^{-1}$; $\delta_H(CDCl_3)$ 1.85 (6 H, d, *J* 0.7 Hz, Me), 6.20 (2 H, q, *J* 0.7 Hz, 3- and 5-H), 7.30 (3 H, m, benzim.), 7.85 (1 H, m, benzim. 4-H), and 8.13 (1 H, s, benzim. 2-H).

*Method B*. A mixture of 1-aminobenzimidazole (5.32 g, 40 mmol) and dehydroacetic acid (6.73 g, 40 mmol) was dissolved in concentrated hydrochloric acid and the solution was refluxed for 24 h. Work-up of the resulting mixture as in Method A, followed by fractional recrystallization from ethanol gave *1-benzimidazol-1-yl-2,6-dimethylpyridin-4(1H)-one* (**9**) (2.29 g, 24%), identical with that obtained from Method A (m.p. and mixed m.p.), and *3-acetyl-1-benzimidazol-1-yl-4-hydroxy-6-methylpyridin-2-one* (**11**) (4.98 g, 44%), m.p. 228—229 °C (Found: C, 64.0; H, 4.9; N, 15.15. $C_{15}H_{13}N_3O_3$ requires C, 63.6; H, 4.6; N, 14.85%) $\nu_{max.}$(KBr) 3 100, 1 725, 1 650, 1 500, 1 245, 1 155, 770, and 760 $cm^{-1}$; $\delta_H(CDCl_3)$ 2.04 (3 H, d, *J* 0.74 Hz, 6-Me), 2.56 (3 H, s, acetyl), 6.69 (1 H, q, *J* 0.74 Hz, 5-H), 7.4 (3 H, m, benzim.), 7.9 (1 H, m, benzim. 4-H), 8.21 (1 H, s, benzim. 2-H), and 16.3 (1 H, br s, OH); *m/z* 283 ($M^+$, 2%) and 119 (100%).

*1-Methyl-3-(1-methyl-1,2,4-triazol-4-ylio)benzimidazolium Bis-(methyl sulphate)* (**1**).—A mixture of 4-(1,2,4-triazol-4-yl)benzimidazole (0.5 g, 2.7 mmol) and dimethyl sulphate (1.5 ml) was heated for 15 min at 120 °C. The resulting solution was cooled to 0 °C and then cool absolute ethanol (15 ml) was added dropwise. The solid crystals formed were filtered off and washed with a small amount of absolute ethanol (0.9 g, 76%), m.p. 160—163 °C (Found: C, 36.0; H, 4.3; N, 15.9. $C_{13}H_{19}N_5O_8S_2$ requires C, 35.7; H, 4.4; N, 16.0%); $\nu_{max.}$(KBr) 3 135, 3 060, 1 635, 1 510, 1 470, 1 300—1 200, 1 090, 1 070, 1 020, 780, 760, 630, and 560 $cm^{-1}$; $\delta_H[(CD_3)_2SO]$ 4.25 (6 H, s, Me), 7.7—8.3 (4 H, m, benzim.), 9.85 (1 H, s, triaz. 3-H), 10.39 (1 H, s, benzim. 2-H), and 10.95 (1 H, s, triaz. 5-H).

*1-Methyl-3-pyrrol-1-ylbenzimidazolium Iodide* (**2**).—A mixture of 1-pyrrol-1-ylbenzimidazole (0.30 g, 1.6 mmol) and methyl iodide (2.0 ml) was heated for 8 h at 100 °C in a sealed tube. After cooling, the mixture was evaporated and the residue recrystallized from methanol–ether (0.14 g, 69%), m.p. 225—228 °C (decomp.) (Found: C, 44.4; H, 3.75; N, 12.85. $C_{12}H_{12}IN_3$ requires C, 44.3; H, 3.7; N, 12.9%); $\nu_{max.}$(KBr) 3 105, 2 930, 1 585, 1 460, 1 440, 1 265, 1 070, 980, 750, and 700 $cm^{-1}$; $\delta_H[(CD_3)_2SO]$ 4.16 (3 H, s, Me), 6.43 (2 H, t, pyrr. 3- and 4-H), 7.44 (2 H, t, pyrr. 2- and 5-H), 8.15 (4 H, m, benzim.), and 10.49 (1 H, s, benzim. 2-H). The same compound can also be obtained in lower yield (24%) by the reaction of 1-amino-3-methylbenzimidazolium iodide with an excess of 2,5-diethoxytetrahydrofuran in acetic acid.

*1,1′-Dimethyl-4,4′-bi-1,2,4-triazolium Di-iodide* (**4**).—This compound was obtained similarly, by heating 4,4′-bi-1,2,4-triazole (0.1 g, 0.7 mmol) for 8 h at 100 °C with methyl iodide (2 ml) in a sealed tube. Evaporation of the mixture, followed by treatment with acetone, gave (**4**) (0.3 g, 100%), m.p. 210—212 °C (decomp.); $\nu_{max.}$(KBr) 3 315, 3 045, 1 580, 1 450, 1 425, 1 230,

1 160, 1 065, 985, 860, and 610 $cm^{-1}$; $\delta_H$[$(CD_3)_2SO$] 4.07 (3 H, s, Me), 9.22 (1 H, s, 3-H), and 10.20 (1 H, s, 5-H); the bistetrafluoroborate salt was obtained as follows: the starting compound (0.2 g) was quaternized with dimethyl sulphate (0.84 ml, 20 min, 100 °C). Ether was added dropwise until the solid separated. The salt was triturated with tetrafluoroboric acid, and anhydrous ethanol was added until crystals began to develop. On cooling, the crystals separated in 50% yield, m.p. 297—299 °C (Found: C, 21.2; H, 2.8; N, 24.4. $C_6H_{10}N_6\cdot(BF_4)$ requires C, 21.2; H, 3.0; N, 24.7%). If these quaternizations were carried out at 150 °C, only 1,4-dimethyl-1,2,4-triazolium iodide (or methyl sulphate) was isolated.

1-*Methyl*-4-*pyrrol*-1-*yl*-1,2,4-*triazolium Iodide* (**5**).—The compound was prepared as above, in a sealed tube, from 4-pyrrol-1-*yl*-1,2,4-triazole (0.2 g, 1.5 mmol) and methyl iodide (2.5 ml, 24 h, 100 °C). The yield was 0.26 g (98%), m.p. 179 °C (from ethanol) (Found: C, 30.8; H, 3.4; N, 19.85. $C_7H_9IN_4$ requires C, 30.45; H, 3.3; N, 20.3%); $\nu_{max.}$(KBr) 3 150, 3 030, 3 010, 1 585, 1 550, 1 480, 1 295, 1 070, 1 000, 900, and 750 $cm^{-1}$; $\delta_H$ [$(CD_3)_2SO$] 4.23 (3 H, s, Me), 6.48 (2 H, t, pyrr. 3- and 4-H), 7.58 (2 H, t, pyrr. 2- and 5-H), 10.00 (1 H, s, triaz. 3-H), and 11.13 (1 H, s, triaz. 5-H).

2,4,6-*Trimethyl*-1-(2-*methylpyrazol*-1-*io*)*pyridinium Bistetrafluoroborate* (**6**).—The starting compound 2,4,6-trimethyl-1-pyrazol-1-ylpyridinium tetrafluoroborate, was quaternized with dimethyl sulphate (1 h, 150 °C), and the anion was exchanged to tetrafluoroborate as described for compound (**4**). The yield was 68%, m.p. 203—205 °C [Found: C, 37.9; H, 4.55; N, 10.9. $C_{12}H_{17}N_3\cdot(BF_4)_2$ requires C, 38.25; H, 4.55; N, 11.15%]; $\nu_{max.}$(KBr) 3 120—3 000, 1 635, 1 565, 1 445, 1 305, 1 150—1 000, and 680 $cm^{-1}$; $\delta_H$ [$(CD_3)_2SO$] 2.50 (6 H, s, 2-and 6-Me), 2.73 (3 H, s, 4-Me), 4.03 (3 H, s, *N*-Me), 7.40 (1 H, t, pyraz. 4-H), 8.15 (2 H, s, 3- and 5-H), and 9.13 (2 H, br s, pyraz. 3- and 5-H).

4-*Methoxy*-2,6-*dimethyl*-1-(2-*methylpyrazol*-1-*io*)*pyridinium Bistetrafluoroborate* (**7**).—The compound was obtained from 2,6-dimethyl-1-pyrazol-1-ylpyridin-4(1*H*)-one (0.1 g, 0.53 mmol) and dimethyl sulphate (0.2 ml, 30 min, 120 °C), after treatment with ether, filtration and anion-exchange to tetrafluoroborate; yield 0.13 g, (64%), m.p. 206—208 °C [Found: C, 36.6; H, 4.25; N, 10.6. $C_{12}H_{17}N_3O\cdot(BF_4)_2$ requires C, 36.7; H, 4.35; N, 10.7%]; $\nu_{max.}$(KBr) 3 080, 3 005, 1 650, 1 575, 1 510, 1 405, 1 400, 1 340, and 1 100—1 000 $cm^{-1}$; $\delta_H$[$(CO_3)_2SO$] 2.44 (6 H, s, Me), 4.00 (3 H, s, *N*-Me), 4.20 (3 H, s, *O*-Me), 7.34 (1 H, t, pyraz. 4-H), 7.78 (2 H, s, 3- and 5-H), 9.03 (2 H, d, pyraz. 3-H) and 9.10 (2 H, d, pyraz. 5-H). After addition of a drop of water, the signals of the n.m.r. spectrum slowly changed to 2.21 (6 H, s), 4.08 (3 H, s), 6.85 (2 H, s), 8.75 (2 H, s) and 8.81 (2 H, s). This corresponds to the monocationic species 1-methyl-2-(1,4-dihydro-2,6-dimethyl-4-oxo-1-pyridyl)pyrazolium (**16**). The compound was not isolated, nor further characterized.

1-(4-*Methoxy*-2,6-*dimethylpyridinio*)-3-*methylbenzimidazolium Bistetrafluoroborate* (**3**).—This compound was obtained in an analogous way to (**7**), in 56% yield, m.p. 233—235 °C [Found: C, 42.95; H, 4.4; N, 9.2. $C_{16}H_{19}N_3O\cdot(BF_4)_2$ requires C, 43.4; H, 4.3; N, 9.5%]. $\nu_{max.}$(KBr) 3 110, 1 650, 1 580, 1 510, 1 450, 1 340, 1 265, 1 210, 1 180, 1 100—1 000, 950, and 760 $cm^{-1}$; $\delta_H$[$(CD_3)_2SO$] 2.40 (6 H, s, Me), 4.26 (3 H, s, *O*-Me), 4.27 (3 H, s, *N*-Me), 7.92 (2 H, s, 3- and 5-H), 7.92 (2 H, m, benzim. 5- and 6-H), 8.10 (1 H, m, benzim. 4-H), 8.34 (1 H, m, benzim. 7-H), and 10.29 (1 H, s, benzim. 2-H). After addition of a drop of water, the signals of the n.m.r. spectrum slowly shifted to 2.15 (6 H, s), 4.20 (3 H, s), 6.89 (2 H, s), 7.86 (3 H, m), 8.15 (1 H, m), and 10.39 (1 H, s), according to the formation of the monocationic species 1-(1,4-dihydro-2,6-dimethyl-4-oxo-1-pyridyl)-3-methylbenzimidazolium (**15**), which was neither isolated nor further characterized.

*Reactions of* 1-*Methyl*-3-(1-*methyl*-1,2,4-*triazol*-4-*ylio*)*benzimidazolium Bis*(*methyl sulphate*) (**1**).—(*i*) *With water.* A sample of (**1**) (0.23 mmol) was dissolved in water–hexadeuteriodimethyl sulphoxide (50:50 v/v; 2 ml). A kinetic run of the transformation was performed, following in the $^1H$ n.m.r. spectrum at 35 °C, changes in the integrals of the benzimidazolyl 2-H signal of the starting compound and of the triazolyl 3-H signal of the final mixture (1-methyl-1,2,4-triazole and 1-methylbenzimidazol-2-one). Pseudo-first order kinetics were found ($k = 7.78 \times 10^{-4}$ $s^{-1}$). No traces of other products, nor of any residual starting material, were detected in the spectrum. The same experiment, with deuterium oxide instead of water gave a value of $k = 4.75 \times 10^{-4}$ $s^{-1}$.

(*ii*) *With sodium methoxide.* A solution of (**1**) (0.50 g, 1.14 mmol) in a freshly prepared sodium methoxide solution (2 mmol in 50 ml of methanol) was stirred for 5 min at room temperature. The solvent was evaporated under reduced pressure and water (25 ml) was added to the residue. Extraction with ether (3 × 25 ml) afforded a solution from which 0.16 g (89%) of 2-methoxy-1-methylbenzimidazole, m.p. 56—57 °C, were isolated.

(*iii*) *With sodium borohydride.* To a solution of (**1**) (0.20 g, 0.48 mmol) in methanol (15 ml), sodium borohydride (0.05 g, 1.2 mmol) was added in small portions. The resulting mixture was stirred for 6 h at room temperature. Two main compounds were detected by t.l.c. Column chromatography (eluant: chloroform) afforded 2-methoxy-1-methylbenzimidazole (0.04 g, 56%). Further elution with methanol gave 1-methylbenzimidazole (0.02 g, 33%).

(*iv*) *With sodium cyanide.* A solution of (**1**) (0.30 g, 0.73 mmol) in aqueous saturated sodium cyanide (30 ml) was stirred at room temperature for 18 h and extracted with chloroform. Evaporation of the extract gave an oily residue which was purified by column chromatography. Elution with chloroform gave 2-cyano-1-methylbenzimidazole (0.09 g, 80%). Further elution with chloroform–methanol (9:1) afforded a small amount of 1-methylbenzimidazol-2-one (0.008 g, 7%). The formation of this by-product can be completely avoided if the reaction is carried out in two phases, a mixture of (**1**) (0.07 g, 0.17 mmol) saturated aqueous sodium cyanide (10 ml), and chloroform (10 ml) being shaken for 10 h. From the organic layer, a quantitative yield (0.03 g) of 2-cyano-1-methylbenzimidazole was obtained.

(*v*) *With diethylamine.* A mixture of (**1**) (0.15 g, 0.36 mmol) and diethylamine (5 ml) in dichloromethane (5 ml) was stirred at room temperature for 24 h. Evaporation of the solvent and excess of the reagent, followed by column chromatography (eluant: chloroform) afforded 2-ethylamino-1-methylbenzimidazole (0.06 g, 78%). If the reaction was carried out in water, (**1**) (0.50 g, 1.21 mmol), diethylamine (1.2 mmol), water (25 ml) room temperature, 3 h, only 1-methylbenzimidazol-2-one (0.13 g, 70%) was isolated.

(*vi*) *With ammonium hydroxide.* A solution of (**1**) (0.30 g, 0.73 mmol) in concentrated ammonium hydroxide (30 ml) was kept for 16 h at room temperature. The solution was extracted with chloroform and the extract was dried and evaporated to give a residue which was purified by column chromatography. Elution with chloroform–ethanol (99:1) afforded bis(1-methylbenzimidazol-2-yl)amine (0.02 g, 12%), m.p. 210—212 °C. Elution with ethanol gave 2-amino-1-methylbenzimidazole (0.05 g, 45%), m.p. 203—206 °C.

*Reactions of* 2,4,6-*Trimethyl*-1-(2-*methylpyrazol*-1-*io*)-*pyridinium Bistetrafluoroborate* (**6**).—(*i*) *With diethylamine.* A solution of (**6**) (0.20 g, 0.53 mmol) in water (10 ml) was mixed

with chloroform (10 ml). A solution of diethylamine (1.6 mmol) in water (10 ml) was added and the whole mixture was shaken for 1 min. The organic layer was separated and the aqueous layer was further extracted with chloroform (2 × 10 ml). The combined extracts were dried and evaporated to give 4-hydroxymethyl-2,6-dimethylpyridine (**19**) (0.04 g, 56%), m.p. 102—103 °C. Evaporation of the aqueous layer gave a residue whose n.m.r. spectrum showed no trace of pyrazoles. Essentially the same result was obained if dilute sodium hydroxide was substituted for diethylamine.

(*ii*) *With sodium cyanide.* Compound (**6**) (0.50 g, 1.33 mmol) was added to a mixture of sodium cyanide (0.06 g, 1.33 mmol), water (20 ml) and chloroform (25 ml), and the mixture was shaken for 1 min; it was then extracted as above. The $^1$H n.m.r. spectrum of the residue (0.11 g) showed it to be a 1 : 1 mixture of collidine (2,4,6-trimethylpyridine) and 5-cyano-1-methylpyrazole (**21**). Traces of hydroxymethyl-2,6-dimethylpyridine (**19**), but not of 3-cyano-1-methylpyrazole (**20**), were also detected. The identification of (**21**) was performed by adding the authentic sample to the solution.

*Reaction of* 1-*Methyl*-3-*pyrrol*-1-*ylbenzimidazolium Iodide* (**2**) *with Sodium Methoxide.*—A solution of (**2**) (0.50 g, 1.54 mmol) in methanolic sodium methoxide (freshly prepared from 0.04 g of sodium and 50 ml of methanol) was allowed to react at room temperature for 5 h. The solvent was removed and the residue dissolved in water and extracted with chloroform. The extract was dried and evaporated, and the residue (0.31 g) submitted to chromatography (eluant: hexane–dichloromethane) giving N-*methyl*-N-(o-*pyrrol*-1-*ylamino-phenyl*)*formamide* (**17**) (0.27 g, 82%), m.p. (after sublimation at 112 °C/0.06 Torr) 122—123 °C (Found: C, 66.75; H, 6.1; N, 19.6. $C_{12}H_{13}N_3O$ requires C, 66.95; H, 6.1; N, 19.5%); $\nu_{max.}$(KBr) 3 225, 3 140, 1 675, 1 600, 1 485, 1 350, 1 255, 1 080, 1 070, 970, 755, and 715 cm$^{-1}$; $\delta_H$($CDCl_3$) (*E*-form) 3.24 (3 H, s, Me), 6.21 (2 H, t, pyrr. 3- and 4-H), 6.73 (2 H, t, pyrr. 2- and 5-H), 6.9—7.2 (4 H, m, benzene), and 8.35 (1 H, s, CHO); (*Z*-form) 3.41, 6.20, 6.76, 6.9—7.2, and 8.35; *m*/*z* 94 (100%), and 215 ($M^+$, 53%).

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