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# Nitroimidazoles: Part VIII—2-Amino-1-methyl-5-nitroimidazoles & Derivatives†‡

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Treatment of 1-methyl-2-methylsulphonyl-5-nitroimidazole (**3**) with liquid ammonia gives 2-amino-1-methyl-5-nitroimidazole (**2**). With sodamide and **3**, the major product is the sulphone (**4**). **2** is transformed by isocyanates into ureas (**5a-c**), while with 2-chloroethyl isocyanate, imidazolidinone (**6**) and aminooxazolinone (**7**) are obtained. **2** is less reactive towards isothiocyanates and gives under forcing conditions, thioureas (**8a, b**) and guanidines (**9a, b**). Amides (**10a-c**) are obtained from **2** by acylation and **10d-g** from sulphone (**3**) by displacement reactions as also sulphamides (**11a-c**). Cyclic anhydrides and **2** lead to imides (**13-15**). **2** is transformed into schiff bases (**16a-k**), some of them being reduced by sodium borohydride to aralkyl amines (**17a-c**). The ethoxymethylene derivative (**18**) of **2** is transformed into a large number of formamidines (**19a-r**), (**20a-c**) and **21**, some of them being further converted into the dichloroacetyl derivatives (**22a-c**). Reaction of **18** with sodium borohydride affords the ethoxymethylamine (**23b**) and methylamine derivative (**23a**). The latter is available from **2** along with dimethylamine (**23c**) by alkylation with methyl iodide. A less satisfactory route for **23a** and **23c** is displacement of sulphone group from **3** by appropriate amine. Analogous displacements on **3** provide the derivatives **23d, e** and **24**. The product from the reaction of **3** with sodium azide is the azido derivative (**25**). The aziridine (**27**) undergoes iodide-catalysed ring opening to form **29a** and does not rearrange to the imidazoline (**28**). The aminoethanol derivative (**29b**) results from **27** by an acid-catalysed reaction.

The outstanding antiprotozoal activity of 1-methylsulphonyl-3-[1-methyl-5-nitroimidazol-2-yl]-2-imidazolidinone (**1**)[1]** led to the synthesis of analogous nitroimidazoles carrying a variety of azaheterocycles[2-4] at position-2. In this context, it was also of interest to prepare 2-amino-1-methyl-5-nitroimidazole (**2**) which was unknown, although an analogous molecule with an extra methyl group at position-4 had been reported in the literature[5]. The present paper describes the synthesis of **2** and a variety of derivatives, with a view to studying the metabolism of **1**. The exercise additionally brings to light some interesting aspects of nitroimidazole chemistry.

2-Amino-1-methyl-5-nitroimidazole (**2**) was prepared by the reaction of 1-methyl-2-methylsulphonyl-5-nitroimidazole (**3**)[1] with liquid ammonia. The use of sodamide in place of ammonia also afforded **2**, but the major product was **4**. The formation of **4** is envisaged to be initiated by the abstraction of a proton from the methyl group of **3** by amide ion. The resulting carbanion then displaces the methylsulphonyl group in a second molecule of **3** to afford **4** (Chart 1). The structure of **4** is supported by analytical and spectral data (see Experimental).

Reaction of **2** with isocyanates afforded the ureas (**5**) in moderate yields. 2-Chloroethyl isocyanate and **2** in the presence of triethylamine gave a mixture of isomeric oxazoline (**7**) and imidazolidinone (**6**) which arose from the chloroethyl urea as an intermediate. **6** and **7** were readily distinguished from each other by their spectral data (see Experimental). The presence of a C=O band in the IR spectrum of **6** at 1740 $cm^{-1}$ was particularly helpful. The identity of **6** was established further by comparison with a sample prepared earlier[2].

In contrast to the facile reaction with isocyanates, **2** was inert towards isothiocyanates under normal conditions. Reaction occurred in the presence of sodium hydride to afford in addition to the expected thioureas (**8**), significant amounts of the guanidines (**9**). The formation of **9** could be rationalised as shown in Chart 2.

Reaction of **2** with acid chlorides gave the expected amides (**10a-c**). An alternative procedure for the synthesis of **10**, namely displacement of the sulphone group in **3** by the ion of an appropriate amide was also used to obtain **10d-g**. Similar displacements using *p*-fluorobenzenesulphonamide, sulphamide and 1, 1, 3-trimethylsulphamide afforded respectively **11a-c**.

The ready availability of **10a** and the well-known antiamoebic properties of diloxanide[6] (N-dichloroacetyl-N-methyl-*p*-aminophenol) made the synthesis of **12a** desirable objective. An attempt to methylate **10a** using diazomethane led to anomalous but interesting results which are presented in separate communications[7,8]. Imides (**13-15**) were synthesised from **2** using appropriate cyclic anhydride.

**2** Readily formed crystalline schiff bases (**16a-k**) with a variety of aromatic and heterocyclic aldehydes.

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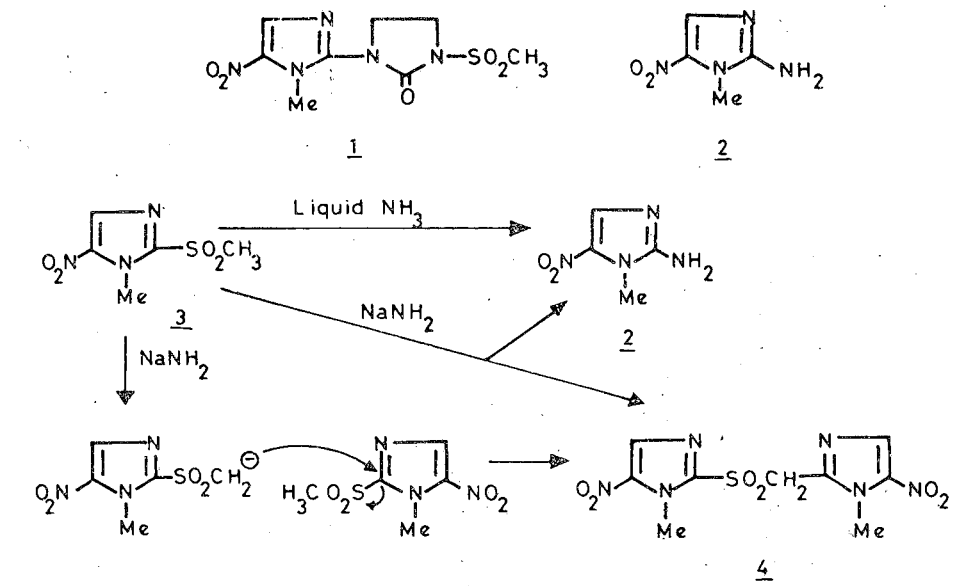


Chart 1

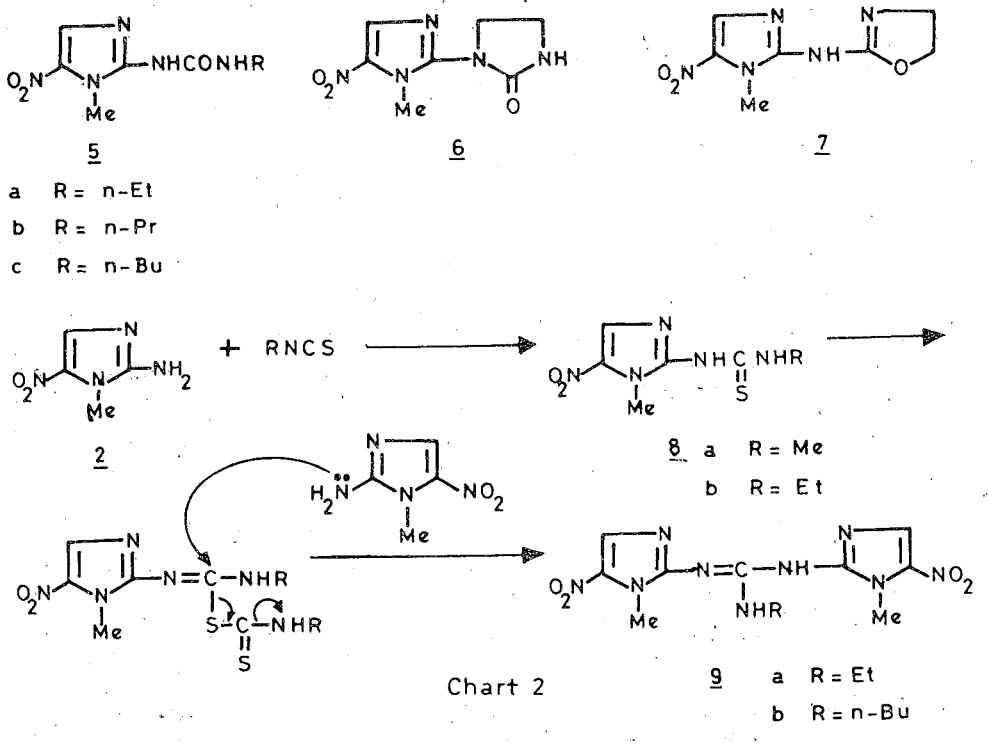


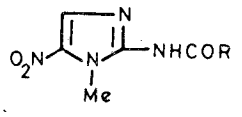
Chart 2

Three of these were reduced by sodium borohydride to give aralkylamines (**17a-c**).

Condensation of **2** with triethyl orthoformate gave the ethoxymethylidene derivative (**18**), which upon further reaction with a large variety of amines was transformed into formamidine (**19**). Substituted ethylenediamine and 1, 3-diaminopropanes furnished upon reaction with **18**, products (**20a-c**), while piperazine gave **21**. **19g, h** and **j** were treated with dichloroacetic anhydride to form the dichloroacetamides (**22a-c**) respectively.

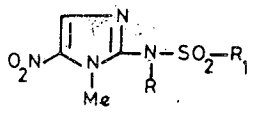
Reduction of **18** with sodium borohydride afforded the amines **23a** and **23b**. **23a** Also became available from **2** along with the dimethyl derivative **23c** by alkylation with methyl iodide using sodium hydride. Displacement of the sulphone group in **3** with mono or dimethylamine was a much poorer alternative although this reaction worked better for aromatic or heteroaromatic amines, **23d** and **e** being obtained readily with 2-aminobenzimidazole was *bis*-heteroaroylated yielding **24**.

Reaction of **3** with sodium azide gave a product,



10

| | R |
|---|---|
| a | $CHCl_2$ |
| b | 2,4-di Cl-$C_6H_3$ |
| c | 3-pyridyl |
| d | 4-$NO_2C_6H_4$ |
| e | 4-$ClC_6H_4$ |
| f | 4-pyridyl |
| g | 2-pyrazinyl |



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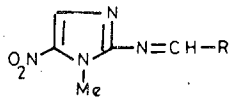
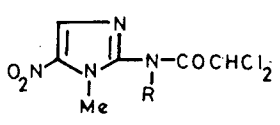
| | R | $R_1$ |
|---|---|---|
| a | H | 4-$FC_6H_4$ |
| b | H | $NH_2$ |
| c | Me | $NMe_2$ |



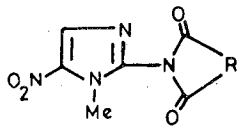
19

| | R | | R |
|---|---|---|---|
| a | –N⟨ ⟩ | j | –NHMe |
| b | –HN–N⟨ ⟩ | k | –N(Me)$CH_2C_6H_5$ |
| c | –HN–N⟨ O ⟩ | l | –NHNHCO$_2$Bu(t) |
| d | –N⟨ N–$CH_3$ ⟩ | m | –N⟨ N–$CH_2$Ph ⟩ |
| e | –N⟨ O ⟩ | n | –NHCH$_2$CO$_2$Et |
| f | –N⟨ ⟩ | o | –N$Me_2$ |
| g | –NH$(CH_2)_2C_6H_4$Cl(4) | p | –N△ |
| h | –NH–$CH_2$–$C_6H_4$Cl(4) | q | –N⟨ N–CO$_2$Et ⟩ |
| i | –$NH_2$ | r | –N(H)△ |



10 a R = H

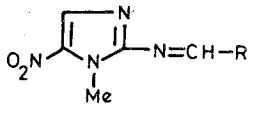
12 R = Me



13 R = $-CH_2CH_2-$

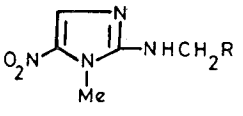
14 R = o-phenylene

15 R = $-(CH_2)_3-$



16

| | R | | R |
|---|---|---|---|
| a | $C_6H_5$ | g | 2-$HOC_6H_4$ |
| b | 4-$NO_2C_6H_4$ | h | 2-HO;3,5 di Cl.$C_6H_2$ |
| c | 4-$ClC_6H_4$ | i | 2-HO;3,5 di Br $C_6H_2$ |
| d | 4-$FC_6H_4$ | j | 2-thienyl |
| e | 2,4-di $ClC_6H_3$ | k | 4-pyridyl |
| f | 4-$AcNHC_6H_4$ | | |



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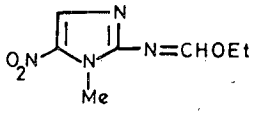
| | R |
|---|---|
| a | $C_6H_5$ |
| b | 4-$NO_2C_6H_4$ |
| c | 2-thienyl |



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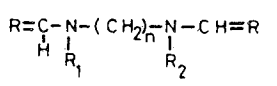

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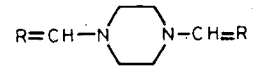
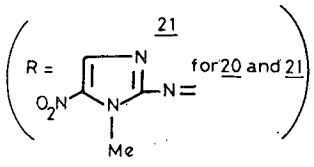
| | | |
|---|---|---|
| a | $R_1 = R_2 = Me$, | n = 2 |
| b | $R_1 = R_2 = Me$, | n = 3 |
| c | $R_1 = H$, $R_2 = CH_2CH_2OH$, | n = 3 |





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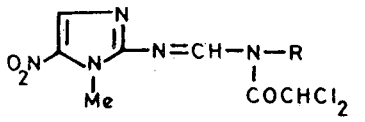
which was readily recognised to be the azide (**25**), the alternative more attractive product, tetrazole (**26**) not being formed (IR band at 2150 $cm^{-1}$). 2-Aziridino-1-methyl-5-nitroimidazole (**27**) obtained from **3** and aziridine was deliberately sought to be isomerised to an imidazoimidazole (**28**). The use of sodium iodide in acetone led only to the iodoethylamine (**29a**), while acid-catalysed opening afforded the aminoethanol (**29b**) reported by us earlier[2].

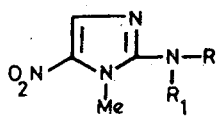
## Experimental Procedure

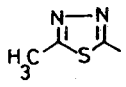
*2-Amino-1-methyl-5-nitroimidazole* (**2**)—1-Methyl-2-methylsulphonyl-5-nitroimidazole[1] (**3**, 40 g) was added in portions to liquid ammonia (500 ml) with stirring and cooling under dry ice-acetone. The mixture was stirred overnight regulating the slow escape of ammonia gas using dry ice-acetone. Before all the ammonia had escaped, ice-cold water (50 ml) was added to the mixture and extracted repeatedly with ethyl acetate. The organic extract was dried ($Na_2SO_4$) and concentrated to a small volume under reduced pressure to afford **2** as an orange yellow solid (25 g), m.p. 205°; $M^+$ 142; PMR ($CDCl_3$): $\delta$ 3.77 (3H, *s*, $N-CH_3$), 7.84 (1H, *s*, C-4H) (Found: C, 34.1; H, 4.6; N, 39.8. $C_4H_6N_4O_2$ requires C, 33.8; H, 4.3; N, 39.4%).

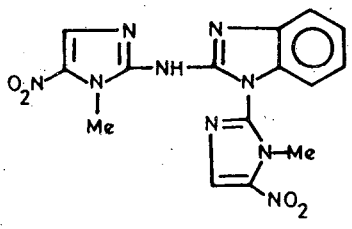
*(1-Methyl-5-nitroimidazol-2-yl)-[(1-methyl-5-nitroimidazol-2-yl)methyl] sulphone* (**4**) *and* **2**—To liquid ammonia (400 ml) kept under nitrogen atmosphere was added with stirring and cooling (dry ice-acetone) sodamide (1.5 g) followed by **3** (6.5 g) in



22 R
a $CH_3$
b $-CH_2C_6H_4Cl(4)$
c $-CH_2CH_2C_6H_4Cl(4)$



23 R $R_1$
a Me H
b $CH_2OEt$ H
c Me Me
d  H
e $4-NO_2C_6H_4$ H



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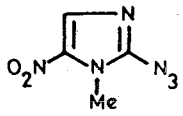

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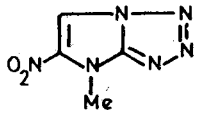

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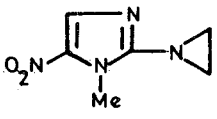

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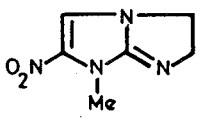

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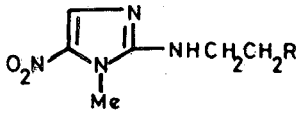

29 a R = I
b R = OH

tetrahydrofuran (THF, 30 ml). The mixture was stirred at the reflux temperature of ammonia for 3 hr, ether (150 ml) added and stirred overnight at room temperature. Ammonium chloride (5 g) was added to the mixture to decompose excess sodamide, the solvent decanted off and the residue extracted with THF. Removal of the solvent from the combined extracts yielded an oily residue (4.4 g) which was chromatographed over silica gel (75 g). The fraction eluted with 3% methanolic chloroform gave a solid which was recrystallised from ethyl acetate-chloroform to afford **4** (800 mg), m.p. 156°; $M^+$ 330 (Found: C, 33.0; H, 3.3; N, 25.6. $C_9H_{10}N_6O_6S$ requires C, 32.7; H, 3.1; N, 25.5%); PMR ($CDCl_3$ + DMSO-$d_6$): $\delta$ 4.08, 4.13 (2*s*, 3H each, $2 \times N-CH_3$), 5.30 ($SO_2CH_2$), 7.88, 8.05 (2*s*, 1H each, $2 \times C_4$-H).

The fractions eluted with 10% methanolic chloroform yielded **2** which recrystallised from ethyl acetate (150 mg), m.p. and m.m.p. with the previous sample 205°.

*General procedure for the preparation of ureas* (**5**)—A mixture of **2** (0.01 mol) alkyl isocyanate (0.015 mol), triethylamine (2 ml) and anhydrous dioxane (40 ml) was boiled under reflux for 18 hr. The solvent was removed under reduced pressure, the residue treated with ice-water and the solid filtered off. Recrystallisation from methylene chloride-ether afforded **5** (see Table 1).

1-(1-*Methyl*-5-*nitroimidazol*-2-*yl*)-2-*imidazolidinone* (**6**) *and* 2-[*N*-(1-*methyl*-5-*nitroimidazol*-2-*yl*)]*amino*-*oxazoline* (**7**)—A mixture of amine **2** (2.1 g), $\beta$-chloroethyl isocyanate (2 ml), triethylamine (5 ml) and dry dioxane (50 ml) was heated under reflux for 30 hr. The solvent was removed under reduced pressure and the residue treated with ice and saturated aq. potassium bicarbonate (20 ml). The solid was filtered off, washed with water and crystallised from methylene chloride-ethanol to yield the aminooxazoline (**7**) as yellow solid, (0.9 g), m.p. 187-89°; $M^+$ 211; PMR (DMSO-$d_6$): $\delta$ 3.72 (3H, *s*, $N-CH_3$), 3.80 (2H, *t*, $N-CH_2$), 4.58 (2H, *t*, $O-CH_2$) and 7.95 (1H, *s*, C-4H) (Found: C, 40.1; H, 4.6; N, 32.9. $C_7H_9N_5O_3$ requires C, 39.8; H, 4.3; N, 33.2%). The aqueous mother liquor was extracted with $CH_2Cl_2$, the solvent evaporated off and the residue chromatographed to obtain **6**[1] (0.5 g), m.p. 203-5°.

*General procedure for the preparation of thioureas* (**8**) *and guanidines* (**9**)—To dry dimethylformamide (DMF, 50 ml) kept under nitrogen atmosphere was added sodium hydride (50%, 0.05 mol) with stirring and cooling. A solution of **2** (0.05 mol) was then added dropwise (during 15 min) at 0° and the mixture stirred at the same temperature for 2 hr after which a solution

Table 1—Derivatives of 1-Methyl-2-amino-5-nitroimidazole

| Compd No. | m.p. (°C) | Crystallised from | Yield (%) | Mol. formula | Analysis (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Calculated | | | Found | | |
| | | | | | C | H | N | C | H | N |
| **5a** | 210-12(d) | $CH_2Cl_2$-$Et_2O$ | 40 | $C_7H_{11}N_5O_3$ | 39.43 | 5.20 | 32.85 | 39.86 | 5.36 | 32.52 |
| **5b** | 212-14(d) | $CH_2Cl_2$-$Et_2O$ | 50 | $C_8H_{13}N_5O_3$ | 42.29 | 5.77 | 30.82 | 42.54 | 6.05 | 31.14 |
| **5c** | 196-98(d) | $CH_2Cl_2$-$Et_2O$ | 40 | $C_9H_{15}N_5O_3$ | 44.80 | 6.27 | 29.03 | 44.87 | 6.46 | 29.38 |
| **8a** | 182-84 | $CH_2Cl_2$-$Et_2O$ | 25 | $C_6H_9N_5O_2S$ | 33.49 | 4.22 | 32.55 | 33.79 | 4.54 | 32.31 |
| **8b** | 179-82(d) | EtOH | 30 | $C_7H_{11}N_5O_2S$ | 36.68 | 4.84 | — | 37.15 | 5.10 | — |
| **9a** | 238-40(d) | EtOH | 15 | $C_{11}H_{15}N_9O_4$ | 39.17 | 4.48 | — | 39.13 | 4.70 | — |
| **9b** | 174-76 | Toluene-hexane | 15 | $C_{13}H_{19}N_9O_4$ | 42.73 | 5.24 | 34.51 | 42.79 | 5.51 | 34.69 |
| **10a** | 186-88(d) | $CH_2Cl_2$-$Et_2O$ | 50 | $C_6H_6Cl_2N_4O_3$ | 28.48 | 2.39 | 22.14 | 28.71 | 2.64 | 22.38 |
| **10b** | 217-19(d) | $CH_2Cl_2$-$Et_2O$ | 40 | $C_{11}H_8Cl_2N_4O_3$ | 41.92 | 2.56 | 17.78 | 42.18 | 2.75 | 17.68 |
| **10c** | 229-31 | $Me_2CO$ | 35 | $C_{10}H_9N_5O_3$ | 48.58 | 3.65 | 28.33 | 48.75 | 3.94 | 27.98 |
| **10d** | 257(d) | DMF-EtOH | 15 | $C_{11}H_9N_5O_5$ | 45.36 | 3.12 | 24.05 | 45.72 | 3.42 | 24.22 |
| **10e** | 191-92 | EtOH | 15 | $C_{11}H_9ClN_4O_3$ | 47.07 | 3.23 | 19.96 | 47.03 | 3.39 | 19.81 |
| **10f** | 234-35 | DMF-MeOH+$Et_2O$ | 14 | $C_{10}H_9N_5O_3$ | 48.58 | 3.65 | 28.33 | 47.54 | 4.00 | 27.90 |
| **10g** | 223-25 | MeOH-EtOAc | 19 | $C_9H_8N_6O_3$ | 43.55 | 3.25 | 33.86 | 43.24 | 3.56 | 33.91 |
| **11a** | 290-96 | $CH_3CN$-$Et_2O$ | 20 | $C_{10}H_9N_4O_4S$ | 40.01 | 3.02 | 18.66 | 39.94 | 2.87 | 18.42 |
| **11b** | 171-72 | MeOH-$Et_2O$ | 13 | $C_4H_7N_5O_4S$ | 21.72 | 3.19 | 31.67 | 22.43 | 3.68 | 30.50 |
| **11c** | 110-12 | $CH_2Cl_2$-$Et_2O$ | 15 | $C_7H_{13}N_5O_4S$ | 31.94 | 4.98 | 26.61 | 31.69 | 5.22 | 26.33 |
| **13** | 218-20 | $CH_2Cl_2$-$Et_2O$ | 60 | $C_8H_8N_4O_4$ | 42.86 | 3.60 | 24.99 | 43.28 | 3.90 | 24.84 |
| **14** | 205-7 | $CH_2Cl_2$-$Et_2O$ | 50 | $C_{12}H_8N_4O_4$ | 52.94 | 2.96 | 20.58 | 53.17 | 3.22 | 20.69 |
| **15** | 202-4 | $CH_2Cl_2$-EtOH | 30 | $C_9H_{10}N_4O_4$ | 45.38 | 4.23 | 23.52 | 45.56 | 4.46 | 23.75 |
| **16a** | 197-9 | EtOAc | 55 | $C_{11}H_{10}N_4O_2$ | 57.38 | 4.38 | 24.34 | 57.68 | 4.71 | 24.19 |
| **16b** | 241-3 | EtOAc | 40 | $C_{11}H_9N_5O_4$ | 48.00 | 3.30 | 25.45 | 48.25 | 3.60 | 25.54 |
| **16c** | 207-9 | EtOAc | 45 | $C_{11}H_9ClN_4O_2$ | 49.91 | 3.43 | 21.17 | 50.05 | 3.61 | 21.21 |
| **16d** | 223-5 | EtOAc | 35 | $C_{11}H_9FN_4O_2$ | 53.22 | 3.65 | 22.57 | 53.50 | 3.80 | 22.18 |
| **16e** | 192-4 | EtOAc | 35 | $C_{11}H_8Cl_2N_4O_2$ | 44.17 | 2.69 | 18.73 | 44.51 | 3.00 | 19.06 |
| **16f** | 262-4 | EtOAc | 30 | $C_{13}H_{13}N_5O_3$ | 54.35 | 4.56 | 24.38 | 54.14 | 4.83 | 24.65 |
| **16g** | 224-7 | EtOAc | 25 | $C_{11}H_{10}N_4O_3$ | 53.66 | 4.09 | 22.76 | 53.42 | 4.20 | 22.44 |
| **16h** | 236-8 | EtOAc | 30 | $C_{11}H_8ClN_4O_3$ | 41.92 | 2.56 | 17.78 | 42.19 | 2.81 | 17.65 |
| **16i** | 262-4 | EtOAc | 35 | $C_{11}H_8Br_2N_4O_3$ | 32.70 | 1.99 | 13.87 | 32.34 | 2.07 | 13.96 |
| **16j** | 196-8 | EtOAc | 45 | $C_9H_8N_4O_2S$ | 45.76 | 3.41 | 23.72 | 46.12 | 3.68 | 23.48 |
| **16k** | 230-2 | EtOAc | 40 | $C_{10}H_9N_5O_2$ | 51.94 | 3.92 | 30.29 | 52.09 | 4.20 | 30.33 |
| **17a** | 152-4 | EtOAc | 65 | $C_{11}H_{12}N_4O_2$ | 56.89 | 5.21 | 24.13 | 56.98 | 5.46 | 24.08 |
| **17b** | 209-11 | EtOAc | 55 | $C_{11}H_{11}N_5O_4$ | 47.65 | 4.00 | 25.26 | 47.38 | 4.33 | 25.49 |
| **17c** | 159-61 | EtOAc | 40 | $C_9H_{10}N_4O_2S$ | 45.38 | 4.23 | 23.52 | 45.69 | 4.58 | 23.69 |
| **19a** | 191-93 | $CH_2Cl_2$-$Et_2O$ | 70 | $C_9H_{13}N_5O_2$ | 48.42 | 5.87 | 31.38 | 48.57 | 5.98 | 31.72 |
| **19b** | 145-47 | $CH_2Cl_2$-$Et_2O$ | 73 | $C_{10}H_{16}N_6O_2$ | 47.61 | 6.39 | 33.32 | 47.65 | 6.57 | 33.37 |
| **19c** | 218-20 | EtOAc | 70 | $C_9H_{14}N_6O_3$ | 42.51 | 5.55 | 33.06 | 42.74 | 5.93 | 33.38 |
| **19d** | 146-48 | $CH_2Cl_2$-$Et_2O$ | 60 | $C_{10}H_{16}N_6O_2$ | 47.61 | 6.39 | 33.32 | 47.56 | 6.68 | 33.08 |
| **19e** | 169-71 | $CH_2Cl_2$-$Et_2O$ | 70 | $C_9H_{13}N_5O_3$ | 45.18 | 5.48 | 29.28 | 45.18 | 5.54 | 29.41 |
| **19f** | 137-39 | $CH_2Cl_2$-$Et_2O$ | 75 | $C_{10}H_{15}N_5O_2$ | 50.62 | 6.37 | 29.52 | 50.69 | 6.72 | 29.78 |
| **19g** | 149-51 | EtOAc | 66 | $C_{13}H_{14}N_5O_2Cl$ | 50.73 | 4.58 | 22.76 | 50.94 | 4.84 | 22.54 |
| **19h** | 154-56 | EtOAc | 78 | $C_{12}H_{12}ClN_5O_2$ | 49.07 | 4.11 | 23.85 | 49.20 | 4.34 | 23.58 |
| **19i** | 168-70 | EtOH | 50 | $C_5H_7N_5O_2$ | 35.50 | 4.17 | 41.41 | 35.84 | 4.52 | 41.80 |
| **19j** | 203-5 | EtOH | 70 | $C_6H_9N_5O_2$ | 39.34 | 4.95 | 38.24 | 39.72 | 5.25 | 38.18 |
| **19k** | 103-5 | Dioxane-$Et_2O$ | 80 | $C_{13}H_{15}N_5O_2$ | 57.13 | 5.53 | 25.63 | 57.14 | 5.75 | 25.96 |
| **19l** | 186-88 | Benzene | 55 | $C_{10}H_{16}N_6O_4$ | 42.25 | 5.67 | — | 42.48 | 5.85 | — |
| **19m** | 159-61 | EtOAc-$Et_2O$ | 65 | $C_{16}H_{20}N_6O_2$ | 58.52 | 6.14 | 25.60 | 58.61 | 6.31 | 25.90 |
| **19n** | 139-41 | EtOAc-$Et_2O$ | 60 | $C_9H_{13}N_5O_4$ | 42.35 | 5.13 | 27.44 | 42.36 | 5.33 | 27.38 |
| **19o** | 176-78 | EtOAc-$Et_2O$ | 60 | $C_7H_{11}N_5O_2$ | 42.63 | 5.62 | 35.52 | 42.44 | 5.69 | 35.32 |
| **19p** | 122-24 | $CH_2Cl_2$-$Et_2O$ | 55 | $C_7H_9N_5O_2$ | 43.07 | 4.65 | 35.89 | 43.45 | 4.83 | 36.08 |
| **19q** | 168-70 | EtOAc-$Et_2O$ | 80 | $C_{12}H_{18}N_6O_4$ | 46.44 | 5.85 | 27.08 | 46.77 | 6.09 | 26.80 |
| **19r** | 120-22 | $Et_2O$ | 75 | $C_8H_{11}N_5O_2$ | 45.93 | 5.30 | 33.48 | 46.23 | 5.60 | 33.28 |
| **20a** | 221-23 | EtOAc-$Et_2O$ | 35 | $C_{14}H_{20}N_{10}O_4$ | 42.85 | 5.15 | 35.70 | 43.15 | 5.46 | 35.70 |
| **20b** | 205-7 | EtOAc-$Et_2O$ | 35 | $C_{15}H_{22}N_{10}O_4$ | 44.33 | 5.46 | — | 44.03 | 5.60 | — |
| **20c** | 174-76 | EtOAc-$Et_2O$ | 30 | $C_{15}H_{22}N_{10}O_5$ | 42.65 | 5.25 | 33.16 | 42.54 | 5.37 | 33.00 |
| **21** | 312 | $CH_3OH$-$Et_2O$ | 30 | $C_{14}H_{18}N_{10}O_4$ | 43.07 | 4.65 | 35.88 | 43.42 | 4.93 | 35.33 |

*Contd*

Table 1—Derivatives of 1-Methyl-2-amino-5-nitroimidazole—*Contd*

| Compd No. | m.p. (°C) | Crystallised from | Yield (%) | Mol. formula | Analysis (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Calculated | | | Found | | |
| | | | | | C | H | N | C | H | N |
| **22a** | 136-38 | $CH_2Cl_2$-$Et_2O$ | 30 | $C_8H_9Cl_2N_5O_3$ | 32.67 | 3.08 | 23.81 | 32.78 | 3.37 | 23.75 |
| **22b** | 149-51 | $Et_2O$ | 30 | $C_{14}H_{12}Cl_3N_5O_3$ | 41.55 | 2.99 | 17.31 | 41.49 | 3.27 | 17.63 |
| **22c** | 138-40 | $CH_2Cl_2$-$Et_2O$ | 25 | $C_{15}H_{14}Cl_3N_5O_3$ | 43.03 | 3.38 | 16.73 | 43.34 | 3.65 | 16.92 |
| **23a** | 162 | $CH_2Cl_2$-$Et_2O$ | 18 | $C_5H_8N_4O_2$ | 38.46 | 5.16 | 35.88 | 38.76 | 5.46 | 36.26 |
| **23b** | 106 | EtOAc-hexane | 5 | $C_7H_{12}N_4O_3$ | 41.99 | 6.04 | 27.99 | 41.64 | 5.90 | 27.72 |
| **23c** | 90-92 | $CH_2Cl_2$-hexane | 25 | $C_6H_{10}N_4O_2$ | 42.35 | 5.92 | 32.93 | 42.27 | 6.26 | 33.10 |
| **23d** | 265-66 | DMF-$Et_2O$ | 5 | $C_7H_8N_6O_2S$ | 35.00 | 3.36 | 34.99 | 35.40 | 3.51 | 34.36 |
| **23e** | 235-36 | MeOH-$Et_2O$ | 11 | $C_{10}H_9N_5O_4$ | 45.63 | 3.45 | 26.61 | 45.96 | 3.69 | 26.78 |
| **24** | 288-89 | DMF-$Et_2O$ | 5 | $C_{15}H_{13}N_9O_4$ | 47.00 | 3.42 | — | 46.85 | 3.75 | — |

of alkyl isothiocyanate (0.055 m) in DMF (10 ml) was added. The mixture was stirred at 0° for 4 hr and at room temperature for 16 hr. Acetic acid (3 ml) in DMF (10 ml) was added dropwise, the solvent removed *in vacuo*, the residue treated with ice-water, the solid obtained filtered off and chromatographed over silica gel. Elution with toluene-hexane (1 : 1) yielded **9** and that with toluene-methylene chloride (1 : 1) afforded **8** (see Table 1).

*General method for the preparation of amides* (**10**): *Method A*—To a solution of **2** (0.015 mol) in dry dioxane (50 ml) was added with stirring the acid chloride (0.017 mol) in dry dioxane (20 ml) followed by triethylamine (3 ml). The mixture was heated under reflux for 12 hr, the solvent evaporated off and the residue treated with ice and aq. potassium bicarbonate. The solid was filtered off, washed with ice-cold water, dried and recrystallised.

The amides (**10a-c**) were prepared by method-A. The physical properties of these amides are recorded in Table 1.

*Method B*—To a suspension of sodium hydride (0.05 mol) in DMF (30 ml) was added dropwise with stirring below 20°, a solution of the aroylamine (0.05 mol) in DMF (50 ml). The mixture was heated with stirring at 60° for 30 min, cooled and **3** (10.2 g) in DMF (30 ml) added dropwise during 10 min. The mixture was heated at 100° for 1 hr, the solvent removed under reduced pressure, the residue dissolved in water containing a few drops of DMF and the solution acidified to *p*H 6.5 to obtain a solid which was filtered off and recrystallised to afford **10**.

The physical data of the amides (**10d-g**) prepared by the above method are presented in Table 1.

*Sulphamides* (**11a-c**)—These were prepared by reacting **3** with sodium salts of *p*-fluorobenzenesulphonamide, sulphamide and 1, 1, 3-trimethylsulphamide respectively by the method-B above. Physical properties of **11a-c** are listed in Table 1.

*General method for the synthesis of imides* (**13-15**)—A mixture of **2** (0.02 mol), the cyclic anhydride (0.035 mol) and triethylamine (5 ml) in dioxane (80 ml) was heated under reflux for 72-90 hr. The solvent was evaporated *in vacuo*, the residue treated with ice and aq. potassium bicarbonate and left overnight in refrigerator. The solid was filtered off, washed with cold water, dried and recrystallised to afford the imide (see Table 1).

*General method for the preparation of schiff bases* (**16**)—A mixture of **2** (0.03 mol), the aldehyde (0.033 mol), trifluoroacetic acid (0.2 g) and dioxane (75 ml) was boiled under reflux for 12 hr. The solvent was removed under reduced pressure, the residue treated with ice and aq. potassium carbonate, the solid filtered off, washed with water and recrystallised to obtain **16** (see Table 1).

*General method for the preparation of 2-aralkylamino-1-methyl-5-nitroimidazole* (**17**)—To a solution of **16** (0.02 mol) in THF (150 ml) cooled to 0° was added with stirring sodium borohydride (400 mg) in portions during 15 min. The mixture was stirred at the same temperature and the progress monitored by TLC (3-4 hr). The solution was acidified with acetic acid to *p*H 6 and the solvent removed under reduced pressure. The residue was treated with ice-water and extracted with ethyl acetate. The organic extract was dried ($Na_2SO_4$), the solvent evaporated *in vacuo* and the residue recrystallised to afford **17** (see Table 1).

*Ethyl N-(1-methyl-5-nitroimidazol-2-yl)formamidate* (**18**)—A mixture of **2** (1.4 g), triethyl orthoformate (20 ml) and trifuloroacetic acid (2 drops) was boiled under reflux for 12 hr. The excess of triethyl orthoformate was removed under reduced pressure and the residue crystallised from dry hexane to afford **18** (1.5 g), m.p. 74°; $M^+$ 198 (Found: C, 42.4; H, 5.2; N, 28.0. $C_7H_{10}N_4O_3$ requires C, 42.4; H, 5.1; N, 28.3%).

*General method of preparation of amidines* (**19**)—A solution of **18** (0.01 mol) and amine (0.011 mol) in dry

benzene (75 ml) was heated under reflux for 4 hr, the solvent evaporated off and the residue crystallised to obtain **19** (see Table 1).

Similarly were prepared **20a-c** and **21** by reacting 2 mol of **18** with 1 mol of appropriate diamine and piperazine respectively.

*General method for the synthesis of N-dichloroacetyl-amidines* (**22**)—To a solution of **19 g**, **h** or **j** (0.01 mol) in dry methylene chloride (100 ml) was added with stirring dichloroacetic anhydride (0.015 mol) in methylene chloride (10 ml). The mixture was stirred at room temperature for 3 days after which it was cooled to 0°, treated with water and stirred at the same temperature for 3 hr. The methylene chloride layer was washed with aq. potassium bicarbonate, dried ($Na_2SO_4$), the solvent evaporated *in vacuo* and the residue chromatographed over silica gel. Elution with toluene gave a solid which recrystallised to yield **22** (Table 1).

1-*Methyl*-2-*methylamino*-5-*nitroimidazole* (**23a**) *and* 2-*ethoxymethylamino*-1-*methyl*-5-*nitroimidazole* (**23b**)—To a solution of **18** (5 g) in THF (300 ml) was added with stirring sodium borohydride (600 mg) and the mixture stirred for 5 hr at room temperature. Acetic acid (1.5 ml) was then added and the solvent removed under reduced pressure at room temperature. The residue was treated with water, extracted with ethyl acetate, the organic extract dried ($Na_2SO_4$) and the solvent removed *in vacuo*. The residue was chromatographed over silica gel (50 g) and the product eluted with chloroform was crystallised from ethyl acetate-hexane to obtain **23b** (0.25 g), m.p. 106°; PMR (DMSO-$d_6$ + $CDCl_3$): $\delta$ 1.22 (3H, *t*, $J$=7 Hz, $-CH_2CH_3$), 3.63 (2H, *q*, $J$=7 Hz, $OCH_2CH_3$), 3.77 (3H, *s*, $N-CH_3$), 4.97 (2H, *d*, $J$=6.5 Hz, $HN-CH_2-O$), 7.87 (1H, *s*, $C_4$-H), 7.89 (1H, *bs*, NH) (Found: C, 41.6; H, 5.9; N, 27.7. $C_7H_{12}N_4O_3$ requires C, 42.0; H, 6.0; N, 28.0%).

The fractions with 1% methanolic chloroform gave **23a** which recrystallised from methylene chloride-ether (0.7 g), m.p. 162°; $M^+$ 156; PMR (DMSO-$d_6$ + $CDCl_3$): $\delta$ 3.00 (3H, *d*, $J$=5 Hz, $NHCH_3$), 3.67 (3H, *s*, $N-CH_3$), 6.67 (1H, broad *d*, $J$=5 Hz, NH), 7.87 (1H, *s*, $C_4$-H) (Found: C, 38.8; H, 5.5; N, 36.3. $C_5H_8N_4O_2$ requires C, 38.5; H, 5.2; N, 35.9%).

2-*Dimethylamino*-1-*methyl*-5-*nitroimidazole* (**23c**) *and* 1-*methyl*-2-*methylamino*-5-*nitroimidazole* (**23a**)—To an ice-cooled suspension of sodium hydride (50%, 3.8 g) in DMF (75 ml) was added dropwise with stirring under $N_2$, during 15 min a solution of **2** (10 g) in DMF (50 ml). The solution was stirred at 0-5° for 1 hr and to this a solution of methyl iodide (11 g) in DMF (25 ml) was added dropwise at 0° during 10 min. The mixture was stirred at the same temperature for 4 hr and at room temperature for 8 hr. The mixture was acidified to *p*H 6 by adding acetic acid and the solvent removed *in vacuo*. The residue was treated with ice and aq. potassium bicarbonate and extracted with ethyl acetate. The ethyl acetate extract was dried ($Na_2SO_4$), the solvent evaporated under reduced pressure and the residue chromatographed over silica gel. The fraction eluted with chloroform-toluene (1 : 1) yielded **23c** which recrystallised from methylene chloride-hexane (3 g), m.p. 90-92°; $M^+$ 170; PMR ($CDCl_3$): $\delta$ 3.00 [6H, *s*, $N(CH_3)_2$], 3.75 (3H, *s*, $N-CH_3$), 7.78 (1H, *s*, $C_4$-H) (Found: C, 42.3; H, 6.3; N, 33.1. $C_6H_{10}N_4O_2$ requires C, 42.4; H, 5.9; N, 32.9%).

The compound eluted with chloroform-methanol (90 : 10) was crystallised from methylene chloride-hexane to afford **23a** (2.3 g); m.p. and m.m.p. with the authentic sample, 162°.

2-*Dimethylamino*-1-*methyl*-5-*nitroimidazole* (**23c**)—To liquid dimethylamine (50 ml) cooled under freezing mixture was added **3** (10 g) with stirring. The mixture was stirred at the same temperature for 6 hr and the excess dimethylamine removed. The residue was treated with ice-cold water and repeatedly extracted with ether. The ether extract was dried ($Na_2SO_4$) and the solvent evaporated under reduced pressure. The residue was filtered through a column of silica gel using toluene as the eluent. The solid obtained was recrystallised from methylene chloride-hexane to yield **23c** (1 g), m.p. and m.m.p. with an authentic sample prepared by the previous method, 90-92°.

1-*Methyl*-2-[(5-*methyl*-1, 3, 4-*thiadiazol*-2-*yl*-)*amino*]-5-*nitroimidazole* (**23d**)—To a suspension of sodium hydride (50%, 2.4 g) in DMF (50 ml) was added dropwise under stirring and cooling (5-10°) a solution of 2-amino-5-methyl-1, 3, 4-thiadiazole (5.8 g) in DMF (70 ml). After the addition was over, the mixture was stirred at room temperature for 2 hr after which a solution of **3** (10.25 g) in DMF (20 ml) was added dropwise at 15-25° and the mixture stirred at room temperature for 4 hr. The solvent was removed *in vacuo*, the residue treated with water and extracted with methylene chloride. Evaporation of the solvent from the methylene chloride extract gave a gummy residue which was chromatographed over silica gel using chloroform-methanol (97 : 3) to afford **23d** (Table 1).

The compounds (**23e**) and (**24**) were similarly prepared. **23e** was obtained as a solid without chromatography whereas **24** had to be chromatographed as above (see Table 1).

2-*Azido*-1-*methyl*-5-*nitroimidazole* (**25**)—To a solution of sodium azide (6.5 g) in water (10 ml) was added dropwise during 15 min, a solution of **3** (10.25 g) in methylene chloride (100 ml) followed by benzyltrimethylammonium chloride (1 g). The mixture was stirred at room temperature for 8 days.

The methylene chloride layer was separated, washed with a small volume of saturated aq. sodium chloride, dried ($Na_2SO_4$) and the solvent evaporated *in vacuo*. The residue was crystallised from ether-hexane to yield **25** (2 g), m.p. 62-64°; $M^+$ 168; IR ($CH_2Cl_2$): 2150 $cm^{-1}$ (azido); PMR ($CDCl_3$): $\delta$ 3.82 (3H, *s*, $N-CH_3$), 7.92 (1H, *s*, $C_4$-H). (Found: C, 28.9; H, 2.7; N, 50.4. $C_4H_4N_6O_2$ requires C, 28.6; H, 2.4; N, 50.0%).

*N-(1-Methyl-5-nitroimidazol-2-yl)aziridine* (**27**)—To a solution of aziridine (5 ml) in dry methylene chloride (40 ml) was added under stirring and cooling (0°), a solution of **3** (5 g) in methylene chloride (30 ml) during 10 min and the mixture stirred at the same temperature for 24 hr. Saturated aq. sodium chloride (10 ml) was added to the mixture and stirred for 5 min. The methylene chloride layer was dried ($Na_2SO_4$), the solvent removed under reduced pressure and the residue crystallised from methylene chloride-ether to yield **27** (1.5 g), m.p. 112-14°; PMR ($CDCl_3$): $\delta$ 2.48 [(4H, *s*, $N(CH_3)_2$], 3.97 (3H, *s*, $N-CH_3$), 7.78 (1H, *s*, $C_4$-H) (Found: C, 43.0; H, 4.8; N, 33.5. $C_6H_8N_4O_4$ requires C, 42.9; H, 4.8; N, 33.3%).

2-(2-*Iodoethylamino*)-1-*methyl*-5-*nitroimidazole* (**29a**)—A mixture of **27** (0.8 g), sodium iodide (600 mg) and dry acetone (60 ml) was heated at 60° for 20 hr. The solvent was removed under reduced pressure, the residue treated with water and extracted with ethyl acetate. The organic extract was dried ($Na_2SO_4$), the solvent evaporated off and the residue crystallised from methylene chloride-ether to afford **29a** (0.4 g), m.p. 111-13°; $M^+$ 296; PMR ($CDCl_3$): $\delta$ 3.48 (2H, *t*, $J$ = 5 Hz, $I-CH_2-$), 3.80 (3H, *s*, $N-CH_3$), 4.00 (2H, *t*, $J$ = 5 Hz, $N-CH_2-$), 5.20 (1H, *bs*, NH), 7.93 (1H, *s*, $C_4$-H) (Found: C, 24.7; H, 3.3; N, 19.1. $C_6H_9IN_4O_2$ requires C, 24.3; H, 3.1; N, 18.9%).

2-(2-*Hydroxyethylamino*)-1-*methyl*-5-*nitroimidazole* (**29b**)—A solution of **27** (200 mg) in methylene chloride (10 ml) containing trifluoroacetic acid (0.4 ml) was heated under reflux for 14 hr. The solvent was evaporated off, the residue treated with ice and aq. potassium bicarbonate and extracted with methylene chloride. Removal of the solvent yielded a semi-solid which was filtered through a column of silica gel using ethylacetate-methylene chloride (1 : 1) as the eluent. The product was crystallised from ethyl acetate-ether to afford **29b** (50 mg), m.p. 152-54°; $M^+$ 186. (Found: C, 38.5; H, 5.7; N, 30.45. $C_6H_{10}N_4O_3$ requires C, 38.71; H, 5.41; N, 30.1%).

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