Studies in Azole Chemistry. Part I. Syntheses and Reactions of Some Imidazole 3-Oxides

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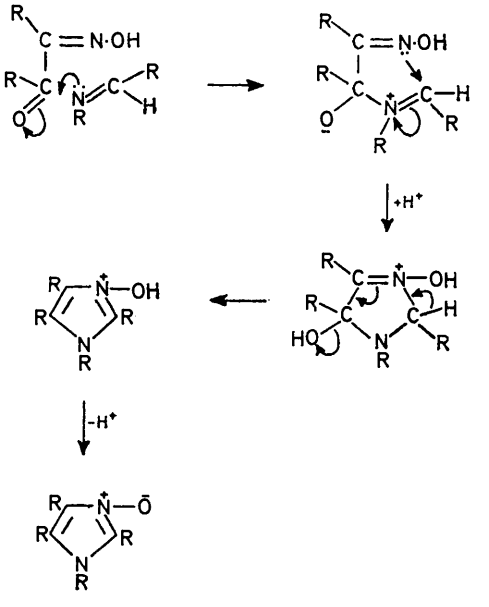
The syntheses are described of 1-benzyl-5-methyl-, 1-benzyl-4,5-dimethyl-, and 1-benzyl-5-hydroxymethyl-4-methyl-imidazole 3-oxide. The first two are deoxygenated by phosphorus trichloride, deoxygenated and chlorinated at C-2 by phosphoryl chloride, and take part in 1,3-dipolar addition reactions. By quaternisation and reaction with cyanide they give 2-cyanoimidazoles.

ALTHOUGH *N*-hydroxyimidazoles have been known for some time,[1] little is known of the simple true imidazole 3-oxides. This is surprising considering the extensive development of the chemistry of benzimidazole 3-oxides.[2] Recently, however, Lettau reported the synthesis of several fully substituted imidazole 3-oxides;[3] these were unsuitable for our purpose of studying the effect of the *N*-oxide function on the reactivity of the imidazole nucleus. We also had found the reaction of an aldehyde, an amine, and an α-diketone mono-oxime in acetic acid (formally represented in the Scheme) to give an imidazole 3-oxide, and we now report the synthesis of examples unsubstituted at C-2 and C-4. Previous attempts[4] to obtain imidazole 3-oxides with unsubstituted ring positions were unsuccessful.

The likely formation of an imine in the first step of the cyclisation reaction suggested the use of preformed imines. Thus, *N*-methylenebenzylamine with biacetyl mono-oxime, pyruvaldehyde monoxime, and 1-acetoxy-3-hydroxyiminobutan-2-one gave the imidazole 3-oxides (1a—c), respectively.

The 3-oxides (1a and b) in the well known procedure for deoxygenation with phosphorus trichloride gave the imidazoles (2a and b), whereas with phosphoryl chloride they gave the 2-chloroimidazoles (3a and b). The Reissert reaction failed to introduce a cyano-group into the imidazole ring, as it does in the pyridine series.[5] However, conversion of (1a and b) into their quaternary derivatives with dimethyl sulphate, and treatment of these salts with potassium cyanide gave the 2-cyanoimidazoles (4a and b). The position of substitution in the 3-oxide (1b) can easily be deduced from the ^{1}H n.m.r. spectra, since the signal from a C-2 proton appears at an appreciably lower field than that from a C-4 proton.

Huisgen[6] has extensively developed 1,3-dipolar cycloadditions, in which heteroaromatic *N*-oxides play the role of 1,3-dipolar compounds reacting with dipolarophiles. This type of reaction has been applied to

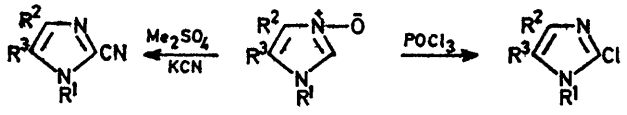


SCHEME

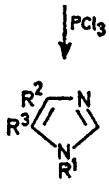
benzimidazole 3-oxides.[7] 1-Benzyl-4,5-dimethylimidazole 3-oxide (1a) reacted with phenyl isocyanate to give principally *N*-(1-benzyl-4,5-dimethylimidazol-2-yl)-*NN'*-diphenylurea (6a), the product of cycloaddition [to give (5)] followed by ring cleavage, decarboxylation, and further reaction with phenyl isocyanate. Quinoxaline

[1] A. R. Katritzky and J. M. Lagowski, 'Chemistry of the Heterocyclic *N*-Oxides,' Academic Press, London, 1971.
[2] H. Lettau, *Z. Chem.*, 1970, **10**, 211.
[3] H. Lettau, *Z. Chem.*, 1970, **10**, 431.
[4] H. Lettau, *Z. Chem.*, 1970, **10**, 462.
[5] T. Okamoto and H. Tani, *Chem. and Pharm. Bull.* (*Japan*), 1959, **7**, 130.
[6] R. Huisgen, *Angew. Chem. Internat. Edn.*, 1963, **2**, 565.
[7] S. Takahashi and H. Kanō, *Chem. and Pharm. Bull.* (*Japan*), 1964, **12**, 1290; 1965, **30**, 1118.

1-oxide behaves similarly.[8] Dimethyl acetylenedicarboxylate reacted readily with the 3-oxides (1a and b)



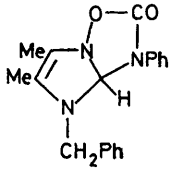
(4a,b) (1a,b,c) (3a,b)



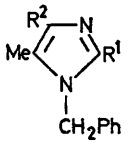
(2a,b)

a; R^1 = $PhCH_2$, R^2 = R^3 = Me
b; R^1 = $PhCH_2$, R^2 = H, R^3 = Me
c; R^1 = $PhCH_2$, R^2 = Me, R^3 = $CH_2 \cdot OH$

to give dimethyl (1-benzyl-4,5-dimethylimidazol-2-yl)- (6b), and dimethyl (1-benzyl-5-methylimidazol-2-yl)-oxalacetate (6c).



(5)



(6)

a; R^1 = NPh·CO·NHPh, R^2 = Me
b; R^1 = $CH(CO_2Me) \cdot CO \cdot CO_2Me$, R^2 = Me
c; R^1 = $CH(CO_2Me) \cdot CO \cdot CO_2Me$, R^2 = H

The mass spectrum of the 1-benzyl-4,5-dimethylimidazole 3-oxide was dominated by the presence of the tropylium ion (*m/e* 91). The 3-oxides (1a and b) showed the expected losses of 16 and 17 mass units from the parent ions.

EXPERIMENTAL

Elemental analyses were performed by Ilse Beetz. I.r. spectra were obtained on a Hilger H90 Infrascan spectrophotometer, low resolution mass spectra on a Perkin-Elmer Hitachi R.M.U. 60 spectrometer, and ^1H n.m.r. spectra (60 and 100 MHz) on a Perkin-Elmer R60 and JEOL JMH/100 spectrometer, respectively. High resolution mass spectra were obtained from the P.C.M.U., Harwell.

1-*Benzyl*-4,5-*dimethylimidazole* 3-*Oxide*.—*N*-Methylenebenzylamine [9] (11·9 g) was added dropwise to a solution of biacetyl mono-oxime (10·1 g) in glacial acetic acid and after 12 h the solution was saturated with dry hydrogen chloride and poured into ether. A semi-solid separated. This was washed with ether, taken up in methanol and precipitated by addition of ether as a fine white solid (12·7 g, 53%). The solution of the salt in water was basified with ammonia (*d* 0·88) and extracted with chloroform. Crystallisation from acetone gave cubes of 1-*benzyl*-4,5-*dimethylimidazole* 3-*oxide* (10·2 g, 51%), m.p. 196—198° (Found: C, 69·6; H, 7·0; N, 13·3%; M^+, 202·1108. $C_{12}H_{14}N_2O$ requires C, 71·2; H, 7·0; N, 13·8%; *M*, 202·1106); τ (60 MHz; $CDCl_3$) 7·93 (3H, s, CH_3), 7·82 (3H, s, CH_3), 5·01 (2H, s, CH_2), 2·75 (5H, m, Ph), and 2·19 (1H, s, CH).

1-*Benzyl*-5-*methylimidazole* 3-*Oxide*.—*N*-Methylenebenzylamine (11·9 g) was added slowly to a stirred solution of pyruvaldehyde monoxime [10] (8·7 g) in glacial acetic acid (20 cm^3) cooled in ice. After 17 h the solution was saturated with dry hydrogen chloride and poured into ether. An oil was obtained which was washed with ether and then dissolved in water (20 cm^3). The solution was basified with ammonia (*d* 0·88) and extracted with chloroform. Removal of the solvent afforded a brown residue. After being washed with ethyl acetate the residue was dissolved in methanol and charcoal was added. After filtration and removal of solvent crystallisation from acetone gave white prisms of 1-*benzyl*-5-*methylimidazole* 3-*oxide* (6·5 g, 35%), m.p. 152° (Found: C, 65·8; H, 6·9; N, 14·0%; M^+, 188·0946. $C_{11}H_{12}N_2O,0{\cdot}7H_2O$ requires C, 65·8; H, 6·7; N, 14·0%. $C_{11}H_{12}N_2O$ requires *M*, 188·0950); τ (60 MHz; $CDCl_3$) 7·89 (3H, s, CH_3), 4·92 (2H, s, CH_2), 3·01 (1H, s, CH), 2·70 (5H, m, Ph), and 1·90 (1H, s, CH).

1-*Benzyl*-5-*hydroxymethyl*-4-*methylimidazole* 3-*Oxide*.—*N*-Methylenebenzylamine (1·8 g) was added to a solution of 1-acetoxy-3-hydroxyiminobutan-2-one [11] (2·4 g) in glacial acetic acid (15 cm^3) stirred and cooled in ice. Stirring at room temperature was continued for 24 h. The solution was saturated with dry hydrogen chloride and poured into ether. The gum obtained was taken up in water and the solution was basified with concentrated ammonia (*d* 0·88). Extraction with chloroform and crystallisation from methanol gave white crystals of 1-*benzyl*-5-*hydroxymethyl*-4-*methylimidazole* 3-*oxide* (1·15 g, 35%), m.p. 184° (Found: C, 65·9; H, 6·4; N, 12·6. $C_{12}H_{14}N_2O_2$ requires C, 66·0; H, 6·5; N, 12·8%); τ (100 MHz; CD_3OD) 7·76 (3H, s, CH_3), 5·52 (2H, s, OCH_2), 4·70 (2H, s, NCH_2), 2·66 (5H, m, Ph), and 1·76 (1H, s, CH); *m/e* 218 (M^+).

1-*Benzyl*-4,5-*dimethylimidazole*.— 1-Benzyl-4,5-dimethylimidazole 3-oxide (0·4 g) was dissolved in chloroform (10 cm^3) and phosphorus trichloride (1·25 g, 0·009 mol) was added dropwise while the solution was stirred and cooled in ice. The solution was then boiled for 1 h, the solvent removed, and the residue poured into water. After adjustment to pH 7·5 with aqueous sodium carbonate the solution was extracted with ether and then with chloroform. Removal of the solvent and sublimation of the residue at 100° and 0·1 mmHg gave needles of 1-*benzyl*-4,5-*dimethylimidazole* (0·225 g, 61%), m.p. 115—117° (Found: C, 77·4; H, 7·3; N, 15·0. $C_{12}H_{14}N_2$ requires C, 77·4; H, 7·5; N, 15·0%); τ (60 MHz; $CDCl_3$) 8·00 (3H, s, CH_3), 7·84 (3H, s, CH_3), 4·98 (2H, s, CH_2), 2·80 (5H, s, Ph), and 2·57 (1H, s, CH); *m/e* 186 (M^+).

1-*Benzyl*-5-*methylimidazole*.— 1-Benzyl-5-methylimidazole 3-oxide (0·376 g) and phosphorus trichloride (1 g) in chloroform (20 cm^3) similarly gave 1-*benzyl*-5-*methylimidazole* (0·302 g, 88%), m.p. 102° (Found: C, 76·7; H, 7·1; N, 16·4. $C_{11}H_{12}N_2$ requires C, 76·7; H, 7·0; N, 16·3%) as white needles after sublimation at 85° and 0·1 mmHg; τ (60 MHz; $CDCl_3$) 7·91 (3H, s, CH_3), 4·95 (2H, s, CH_2), 3·18 (1H, s, CH), 2·80 (5H, m, Ph), and 2·33 (1H, s, CH).

1-*Benzyl*-2-*chloro*-4,5-*dimethylimidazole*.—1-Benzyl-4,5-dimethylimidazole 3-oxide (1 g) was added in portions to phosphoryl chloride (3·0 g) chilled in ice. The solution was

[8] C. Iijima, *J. Pharm. Soc. Japan*, 1967, **87**, 164.
[9] S. H. Pine and B. L. Sanchez, *J. Org. Chem.*, 1971, **6**, 829.
[10] P. Freon, *Ann. Chim.* (*France*), 1939, **11**, 453.
[11] O. Diels and M. Farkas, *Ber.*, 1910, **43**, 1959.

then boiled for 0·5 h, cooled, poured on to ice, and basified with concentrated ammonia. Extraction with chloroform, removal of the solvent, and sublimation (85° and 0·1 mmHg) afforded white prisms of *1-benzyl-2-chloro-4,5-dimethylimidazole* (0·78 g, 72%), m.p. 98° (Found: C, 65·1; H, 6·0; N, 12·8. $C_{12}H_{13}ClN_2$ requires C, 65·3; H, 6·0; N, 12·7%); τ (60 MHz; $CDCl_3$) 8·00 (3H, s, CH_3), 7·88 (3H, s, CH_3), 4·98 (2H, s, CH_2), and 2·75 (5H, m, Ph); *m/e* 220/222 (M^+).

1-Benzyl-2-chloro-5-methylimidazole.—1-Benzyl-5-methylimidazole 3-oxide (0·5 g) and phosphoryl chloride (2·5 cm³) similarly afforded *1-benzyl-2-chloro-5-methylimidazole* (0·31 g, 55%), m.p. 93° (Found: C, 63·7; H, 5·4; N, 13·7. $C_{11}H_{11}ClN_2$ requires C, 63·9; H, 5·4; N, 13·6%), as white needles after crystallisation from petroleum–benzene or sublimation (80° and 0·1 mmHg); τ (60 MHz; $CDCl_3$) 7·89 (3H, s, CH_3), 4·93 (2H, s, CH_2), 3·28 (1H, s, CH), and 2·80 (5H, m, Ph); *m/e* 206/208 (M^+).

1-Benzyl-4,5-dimethylimidazole-2-carbonitrile.— Dimethyl sulphate (0·63 g) and 1-benzyl-4,5-dimethylimidazole 3-oxide (1·01 g) were warmed together on a steam-bath for 2 h. After cooling and washing with ether the product was dissolved in water (2 cm³). A solution of potassium cyanide (0·98 g) in water (10 cm³) was added, the temperature being held between 0 and 5° during the addition. After stirring for 4 h the solution was extracted with chloroform and next day the aqueous solution was again extracted with chloroform. The extracts were combined; removal of solvent gave, as a white powder from chloroform–petroleum, the *nitrile* (0·68 g, 65%), m.p. 125° (Found: C, 73·9; H, 6·4; N, 20·0. $C_{13}H_{13}N_3$ requires C, 73·9; H, 6·2; N, 19·9%); $\nu_{max.}$ 2207 cm⁻¹ (C≡N); τ (60 MHz; $CDCl_3$) 7·92 (3H, s, CH_2), 7·82 (3H, s, CH_3), 4·80 (2H, s, CH_2), and 2·80 (5H, m, Ph); *m/e* 211 (M^+).

1-Benzyl-5-methylimidazole-2-carbonitrile.— 1-Benzyl-5-methylimidazole 3-oxide (0·94 g) treated with dimethyl sulphate (0·63 g) as above gave, after 25 h, the nitrile (0·74 g, 75%), m.p. 113—115° (from petroleum). Sublimation at 95° and 0·1 mmHg gave small white needles, m.p. 113—115° (Found: C, 73·0; H, 5·7; N, 21·4. $C_{12}H_{11}N_3$ requires C, 73·0; H, 5·6; N, 21·3%); $\nu_{max.}$ 2250 cm⁻¹ (C≡N); τ (60 MHz; $CDCl_3$) 7·85 (3H, s, CH_3), 4·75 (2H, s, CH_2), 3·04 (1H, s, CH), and 2·75 (5H, m, Ph); *m/e* 197 (M^+).

Reaction of 1-Benzyl-4,5-dimethylimidazole 3-Oxide with Phenyl Isocyanate.—Phenyl isocyanate (1·19 g) was added dropwise to a stirred solution of the imidazole 3-oxide (2·02 g) in chloroform (5 cm³) cooled in ice. The solution was left for 72 h at room temperature and the solvent was then removed. An oil was obtained which on addition of methanol (5 cm³) gave a white crystalline solid (A) (0·675 g). The residue obtained by removal of the methanol was treated with ethyl acetate (5 cm³) and acetone (2 cm³) to give a precipitate of starting material (0·75 g), identified by m.p. and ^1H n.m.r. spectra. Compound (A) was triturated with methanol and dried to give white needles, m.p. 237—238° (Found: C, 75·2; H, 6·0; N, 14·0. $C_{25}H_{24}N_4O$ requires C, 75·7; H, 6·1; N, 14·1%); $\nu_{max.}$ 3300 (N–H) and 1645 cm⁻¹ (C=O), considered to be N-(*1-benzyl-4,5-dimethylimidazol-2-yl*)-NN′-*diphenylurea* (6a).

Dimethyl (1-Benzyl-4,5-dimethylimidazol-2-yl)oxalacetate.—Dimethyl acetylenedicarboxylate (0·71 g) was added dropwise with stirring to an ice-cooled solution of 1-benzyl-4,5-dimethylimidazole 3-oxide (1·01 g) in chloroform (10 cm³). After stirring for 2 h at room temperature the solvent was removed and ethyl acetate (10 cm³) was added to the residue; the product (1·42 g, 83%) separated. Crystallisation from methanol gave, as a white powder, the *imidazolyloxalacetate* (6b), m.p. 210° (decomp.) (Found: C, 62·4; H, 5·8; N, 8·1. $C_{18}H_{20}N_2O_5$ requires C, 62·8; H, 5·9; N, 8·1%); τ [100 MHz; $(CD_3)_2SO$] 8·0 (3H, s, CH_3), 7·84 (3H, s, CH_3), 6·57 (3H, s, OCH_3), 6·33 (3H, s, OCH_3), 4·91 (2H, s, CH_2), and 2·80 (6H, m, Ph and CH).

Dimethyl (1-Benzyl-5-methylimidazol-2-yl)oxalacetate.—1-Benzyl-5-methylimidazole 3-oxide (0·94 g) and dimethyl acetylenedicarboxylate (0·71 g) similarly gave the *imidazolyloxalacetate* (6c) (1·08 g, 66%), m.p. 196° (decomp.) (Found: C, 62·2; H, 5·5; N, 8·5. $C_{17}H_{18}N_2O_5$ requires C, 61·8; H, 5·5; N, 8·5%) as a white powder (from methanol); τ (100 MHz; CD_3OD) 7·88 (3H, s, CH_3), 6·52 (3H, s, OCH_3), 6·21 (3H, s, OCH_3), 4·82 (2H, s, CH_2), and 2·80 (7H, m, Ph and 2CH).

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