Convenient Syntheses of 2,4(5)-Dialkylimidazoles and 1-Methyl-2,4-dialkylimidazoles

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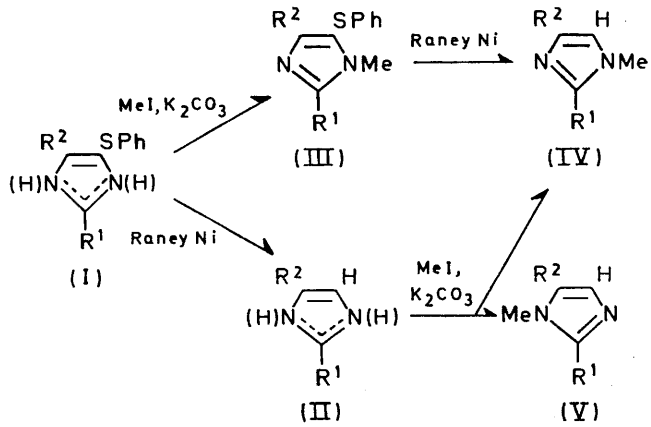
Treatment of 2,4(5)-dialkyl-5(4)-phenylthioimidazoles with Raney nickel produced 2,4(5)-dialkylimidazoles. Methylation of 2,4(5)-dialkyl-5(4)-phenylthioimidazoles yielded 1-methyl-2,4-dialkylimidazoles, whereas methylation of 2,4(5)-dialkylimidazoles yielded in each case two isomers, the 1-methyl-2,4-dialkylimidazole and the 1-methyl-2,5-dialkylimidazole, which were not separated.

THE imidazole ring is present in many natural products. Because of the physiological importance of this system there have been many studies on its synthesis,[1] but no single, widely applicable procedure is yet available. Several methods of synthesis of 2,4(5)-disubstituted imidazoles have been developed, but in all cases yields are poor.[2]

There are many reports on *N*-alkylation of imidazoles,[3] but few of the procedures described have been selective. Pyman *et al.*[4] obtained 1,4-dimethylimidazole and 1,5-dimethylimidazole by methylation of 4(5)-methylimidazole, and separated them by distillation. Allsebrood *et al.*[5] obtained 1,5-dimethyl-4-nitroimidazole and 1,4-dimethyl-5-nitroimidazole by methylation of 2-methyl-4(5)-nitroimidazole under different reaction conditions. Šunjić *et al.*[6] synthesized various 1-alkyl-2-methyl-5-nitroimidazoles and 1-alkyl-2-methyl-4-nitroimidazoles, and Brossi *et al.*[7] obtained 1-isopropyl-2-methyl-5-nitroimidazole and 1-isopropyl-2-methyl-4-nitroimidazole from 2-methyl-4(5)-nitroimidazole.

We have previously reported the syntheses of 2,4(5)-dialkyl-5(4)-phenylthioimidazoles from alkyl nitrones[8] and two 2,4(5)-dialkylimidazoles.[9] Bestmann *et al.*[10] obtained 2-ethyl-4-methyl-5-phenylthioimidazole, but did not attempt to cleave the carbon–sulphur bond. This paper reports convenient methods for the syntheses



a; R^1 = Me, R^2 = Et
b; R^1 = Me, R^2 = Pr^i
c; R^1 = Et, R^2 = Et
d; R^1 = Et, R^2 = Pr^n
e; R^1 = Pr^n, R^2 = Me
f; R^1 = Pr^n, R^2 = Et
g; R^1 = Pr^n, R^2 = Pr^n
h; R^1 = Pr^i, R^2 = Me
i; R^1 = Pr^i, R^2 = Et
j; R^1 = Pr^i, R^2 = Pr^n
k; R^1 = Pr^i, R^2 = Pr^i
l; R^1 = $[CH_2]_{10}\cdot CH_3$, R^2 = Pr^i

of 2,4(5)-dialkylimidazoles and 1-methyl-2,4-dialkylimidazoles.

2,4(5)-Dialkyl-5(4)-phenylthioimidazoles (I), obtained

[1] M. R. Grimmett, *Adv. Heterocyclic Chem.*, 1970, **12**, 103.
[2] A. Windaus and W. Langenbeck, *Ber.*, 1922, **55**, 3706.
[3] K. Hofmann, in 'The Chemistry of Heterocyclic Compounds,' ed. A. Weissberger, Part I, Interscience, New York, 1953.
[4] F. L. Pyman, *J. Chem. Soc.*, 1910, **97**, 1814; 1922, **121**, 2616.
[5] W. E. Allsebrook, J. M. Gulland, and L. F. Story, *J. Chem. Soc.*, 1942, 232.
[6] F. Kajfež, V. Šunjić, D. Kolbah, T. Fajdiga, and M. Oklobdžija, *J. Medicin. Chem.*, 1968, **11**, 167.
[7] M. Hoffer, M. Mitrovic, A. Beaman, and A. Brossi, *J. Medicin. Chem.*, 1971, **14**, 993.
[8] M. Masui, C. Yijima, and K. Suda, *Chem. Comm.*, 1968, 1400.
[9] M. Masui, K. Suda, M. Yamauchi, and C. Yijima, preceding paper.
[10] H. J. Bestman and E. Singer, in 'Newer Methods of Preparative Organic Chemistry,' ed. W. Foerst, Academic Press, New York, 1964, vol. 3, p. 487.

as reported previously,[9] were refluxed in ethanol with Raney nickel (W-2) to give 2,4(5)-dialkylimidazoles (II) in high yield (Table 1). The i.r. spectra of the products (II) showed the characteristic absorptions of the imidazole ring at 2300—3200 cm^{-1}. In the n.m.r. spectra (Table 3), an NH signal (which disappeared on addition of D_2O), and an olefinic proton signal were observed.

When compounds (I) were refluxed in methanol with methyl iodide, and the resulting *N*-methyl product was treated with Raney nickel, 1-methyl-2,4-dialkylimidazoles (IV) were obtained (Table 2). The *N*-methylation also occurred at room temperature, but so slowly that the yield was poor even after 4 days (for $R^1 = R^2 = Pr^i$). In the n.m.r. spectrum of compound (IVk), the signal at τ 3·74 due to the olefinic C-5 proton appeared as a doublet, owing to long-range coupling with the methyne proton of the C-4 isopropyl group. The *N*-methyl signal appeared as a singlet at τ 6·53. The two isopropyl groups exhibited a broad multiplet ($2 \times Me_2CH$) centered at τ 7·13 and a triplet (actually two doublets which partially overlap) ($4 \times Me$) centred at τ 8·79. The n.m.r. data for compounds (IV) are shown in Table 3.

Structure (IV) was assigned on the following bases. When 2,4(5)-di-isopropylimidazole (IIk) was treated with methyl iodide in the same way as compounds (I), the expected *N*-methyl product was not obtained.

TABLE 1

2,4(5)-Dialkylimidazoles (II)

	B.p. (mmHg)	Yield (%)	Found C	Found H	Found N	Formula	Required C	Required H	Required N
(IIa)	128—131° (1)	56	48·0	6·05	13·95	$C_8H_{12}N_2O_4$ [a]	48·0	6·05	14·0
(IIb)	(111·5—112·5) *	77	67·85	9·75	22·35	$C_7H_{12}N_2$	67·7	9·75	22·55
(IIc)	153—160 (4)	64	50·35	6·45	13·0	$C_9H_{14}N_2O_4$ [b]	50·45	6·6	13·1
(IId)	152—155 (3)	83	52·35	7·3	12·2	$C_{10}H_{16}N_2O_4$ [c]	52·6	7·05	12·25
(IIe)	141—145 (4)	66	50·75	6·6	13·0	$C_9H_{14}N_2O_4$ [d]	50·45	6·6	13·1
(IIf)	(66—67) *	60	53·1	7·0	12·2	$C_{10}H_{16}N_2O_4$ [e]	52·6	7·05	12·25
(IIg)	148—152 (0·03—0·04)	49	54·6	7·35	11·7	$C_{11}H_{18}N_2O_4$ [f]	54·55	7·5	11·55
(IIh)	(124—126) *	75	67·65	9·7	22·3	$C_7H_{12}N_2$	67·7	9·75	22·55
(IIi)	(117·5—119·0) *	74	69·3	10·15	20·0	$C_8H_{14}N_2$	69·5	10·2	20·25
(IIj)	(83·0—84·5) *	81	70·9	10·85	18·35	$C_9H_{16}N_2$	71·0	10·6	18·4
(IIk)	(142—144) *	79	70·95	10·5	18·4	$C_9H_{16}N_2$	71·0	10·6	18·4
(IIl)	150—155 (0·03—0·04)	89	77·3	12·15	10·35	$C_{17}H_{32}N_2$	77·2	12·2	10·6

* M.p.

[a] Oxalate, m.p. 140—141°. [b] Oxalate, m.p. 90—91°. [c] Oxalate, m.p. 110—111°. [d] Oxalate, m.p. 158·5—159·0°. [e] Oxalate m.p. 122·0—123·5°. [f] Oxalate, m.p. 104—106°.

TABLE 2

1-Methyl-2,4-dialkylimidazoles (IV)

	B.p. (mmHg)	Yield (%)	Picrate Found C	Found H	Found N	Formula	Required C	Required H	Required N	M.p.
(IVa)	113—115° (20)	73	44·3	4·3	19·65	$C_{13}H_{15}N_5O_7$	44·2	4·3	19·85	127—128°
(IVb)	115—120 (20)	87	45·95	4·75	18·8	$C_{14}H_{17}N_5O_7$	45·75	4·65	19·05	112—114
(IVc)	110—114 (10)	81	46·1	4·6	18·85	$C_{14}H_{17}N_5O_7$	45·75	4·65	19·05	99—100
(IVg)	95—100 (3)	93	48·7	5·35	17·5	$C_{16}H_{21}N_5O_7$	48·6	5·3	17·7	95—95·5
(IVh)	115—123 (30)	94	45·7	4·7	18·85	$C_{14}H_{17}N_5O_7$	45·75	4·65	19·05	144—145
(IVi)	110—115 (10)	84	47·3	4·95	18·25	$C_{15}H_{19}N_5O_7$	47·25	5·0	18·35	130—131
(IVj)	105—115 (9)	87	48·1	5·25	17·5	$C_{16}H_{21}N_5O_7$	48·6	5·3	17·7	88—89
(IVk)	120—130 (15)	90	48·65	5·5	17·65	$C_{16}H_{21}N_5O_7$	48·6	5·3	17·7	155—157

TABLE 3

N.m.r. spectral data for compounds (II) and (IV) (in CCl_4; τ values; J/Hz in parentheses)

	(II) =CH	(II) 2-Me	(II) 4(5)-Me	(IV) =CH	(IV) *N*-Me	(IV) 2-Me	(IV) 4-Me
a	3·53 (t, 1·0)	7·73 (s)		3·74 (t, 1·0)	6·63 (s)	7·88 (s)	
b	3·55 (d, 1·0)	7·69 (s)		3·70 (d, 1·0)	6·56 (s)	7·81 (s)	
c				3·71 (t, 1·0)	6·54 (s)		
d	3·51br (s)						
e	3·52 (q, 1·2)		7·88 (d)				
f	3·51br (s)						
g	3·51br (s)			3·70 (t, 0·7)	6·55 (s)		
h	3·51br (s)		7·89 (s)	3·74 (q, 1·0)	6·53 (s)		7·97 (d, 1·0)
i	3·50br (s)			3·73 (t, 1·0)	6·52 (s)		
j	3·52br (s)			3·73 (t, 0·9)	6·53 (s)		
k	3·50br (s)			3·74 (d, 1·0)	6·53 (s)		
l	3·51br (s)						

Instead the product seemed to be a quaternary salt. It was soluble in chloroform and water and could not be recrystallized from various solvents. On the other hand, when compound (IIk) was dissolved in methanol with methyl iodide–potassium carbonate and the mixture was kept at room temperature for 3 days, the *N*-methyl product (homogeneous on t.l.c.) was obtained. However the n.m.r. spectrum showed that the product was composed of two isomers. These were not separated. From the spectrum the amount of isomer (IVk) was judged to be four times that of isomer (Vk). It seems likely that even if *N*-methylation can occur at both nitrogen atoms of (IIk), the major product is (IVk) because of steric hindrance by the isopropyl groups. In *N*-methylimidazoles, it is known [1,11] that the ring proton adjacent to the methylated nitrogen atom gives a signal at a higher field than the ring proton of the parent imidazoles. The ring proton of compound (IVk) gave a signal at τ 3·74, whereas that of (Vk) was at τ 3·56, close to that (τ 3·50) of the ring proton of the parent (IIk). Thus compounds (IVk) and (Vk) seem to be 1-methyl-2,4-di-isopropylimidazole and 1-methyl-2,5-di-isopropylimidazole, respectively. The compositions of the isomeric mixtures resulting from methylation of compounds (II) are shown in Table 4.

The structure–reactivity relationship was examined as follows. When the same methylation and desulphurization were carried out on 2,4(5)-di-isopropyl-5(4)-phenylsulphonylimidazole (VI), compounds (IVk) and (Vk)

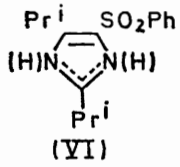
TABLE 4

Compositions of the mixtures resulting from methylation of compounds (II) with methyl iodide–potassium carbonate

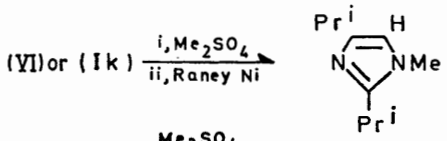
(II)	(IV) (%)	(V) (%)
a	85	15
b	*ca.* 100	Trace
c	94	6
d	88	12
g	94	6
h	72	28
i	87	13
j	89	11
k	78	22

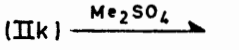
were obtained in the ratio of 93 : 7. Methylation of compounds (Ik), (IIk), and (VI) with dimethyl sulphate, and of the sodium salt of (IIk) with methyl iodide, produced only (IVk). The butylation of compound (IIj) by treatment with n-butyl iodide–potassium carbonate and of (Ij) by treatment with n-butyl iodide–potassium carbonate and then with Raney nickel produced only 1-n-butyl-2-isopropyl-4-n-propylimidazole (VII).

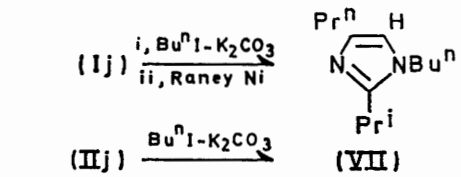
In the case of 4(5)-nitroimidazole, it has been suggested [12] that the electron-withdrawing effect of the nitro-group decreases the basicity of the nearer nitrogen atom so that alkylation occurs predominantly at the further nitrogen atom (S_E2cB) in alkaline media, and at the nearer nitrogen atom (S_E2') in acidic or neutral media. Application of this principle, *i.e.* that the electronic effect of the substituent determines the tautomer ratio, to dialkylimidazoles (II), cannot explain the result that the predominant product is (IV) in all



(VI)

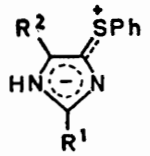




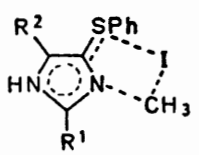


cases. The electronic preference must be overcome by a steric effect. The facts that compound (IIk) gave only (IVk) on treatment with dimethyl sulphate, that (IIk) gave (IVk) and (Vk) on treatment with methyl iodide, and that (IIj) gave only (VII) on treatment with n-butyl iodide, suggest that the size of the alkylating reagent determines the direction of *N*-alkylation.

It seems likely that the ratio of (IV) to (V) would increase with increase in the size of the alkyl substituents. However, the results in Table 4 do not completely support this hypothesis, probably owing to the inadequacy of the procedure used for isolation of the products on which the n.m.r. spectral analysis was carried out. With sulphur-containing compounds (I), a form such as (VIII) might be the reacting species. The positively charged sulphur atom attracts the negative halogen atom of the alkyl halide, and then alkylation takes place at the nitrogen atom near the sulphur *via* a five-membered intermediate (IX).



(VIII)



(IX)

EXPERIMENTAL

I.r. absorption spectra were recorded with a Hitachi ETI-G3 spectrometer, and n.m.r. spectra with a Hitachi–Perkin-Elmer R-20A spectrometer.

[11] G. B. Barlin and T. J. Batterham, *J. Chem. Soc.* (*B*), 1967, 516.

[12] A. Grimison, J. H. Ridd, and B. V. Smith, *J. Chem. Soc.*, 1960, 1352, 1357, 1363.

2,4(5)-*Dialkyl*-5(4)-*phenylthioimidazoles*.—In addition to the compounds described in ref. 9 the following (new) compounds were synthesized: 2,4(5)-*diethyl*-5(4)-*phenylthioimidazole* (Ic), m.p. 159·5—161·5° (Found: C, 67·35; H, 6·9; N, 11·85. $C_{13}H_{16}N_2S$ requires C, 67·3; H, 6·95; N, 12·05%); 4(5)-*methyl*-5(4)-*phenylthio*-2-*n*-*propylimidazole* (Ie), m.p. 188·5—189·5° (Found: C, 67·1; H, 6·85; N, 12·0. $C_{13}H_{16}N_2S$ requires C, 67·3; H, 6·95; N, 12·05%); 4(5)-*ethyl*-5(4)-*phenylthio*-2-*n*-*propylimidazole* (If), m.p. 163·5—164·5° (Found: C, 68·6; H, 7·55; N, 11·5. $C_{14}H_{18}N_2S$ requires C, 68·35; H, 7·4; N, 11·4%); 2-*isopropyl*-4(5)-*methyl*-5(4)-*phenylthioimidazole* (Ih), m.p. 201·5—203·0° (Found: C, 67·5; H, 6·9; N, 11·85. $C_{13}H_{16}N_2S$ requires C, 67·3; H, 6·95; N, 12·05%); 4(5)-*isopropyl*-5(4)-*phenylthio*-2-*undecylimidazole* (Il), m.p. 96—97° (Found: C, 74·05; H, 9·9; N, 7·55. $C_{23}H_{36}N_2S$ requires C, 74·15; H, 9·75; N, 7·5%).

2,4(5)-*Dialkylimidazoles*. *General Method*.—A mixture of 2,4(5)-dialkyl-5(4)-phenylthioimidazole (I), excess of Raney nickel (W-2), and ethanol was refluxed for 5 h. The mixture was filtered off and evaporated and the residue was subjected to silica gel chromatography. 2,4(5)-Dialkylimidazoles were eluted by chloroform–methanol (5 : 3 v/v) (Table 1).

1-*Methyl*-2,4(5)-*dialkylimidazoles*. *General Method*.—A mixture of compound (I) (5 mmol), methyl iodide (15 mmol), potassium carbonate (7 mmol), and methanol (10 ml) was refluxed for 5 h. The solvent was evaporated off and the residue was mixed with water and extracted with chloroform. The extract was dried (Na_2SO_4) and distilled, and the residue was refluxed with a large excess of Raney nickel in ethanol in the usual way to obtain the 1-methyl-2,4-dialkylimidazole (Table 2).

Methylation of Compounds (II) *with Methyl Iodide–Potassium Carbonate*. *General Method*.—A mixture of compound (II) (1 mmol), methyl iodide (3 mmol), and potassium carbonate (1·3 mmol) in methanol (3 ml) was set aside at room temperature for 3—5 days. The solvent was evaporated off and the residue was mixed with water and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated to yield two *N*-methylated products which had the same R_F value on t.l.c. The compositions of the mixtures are shown in Table 4.

Methylation of Compound (IIk).—(a) *With methyl iodide–sodium*. Sodium (23 mg) was dissolved in methanol (2 ml) and compound (IIk) (131 mg) was added. The mixture was evaporated to dryness and the resulting sodium salt was refluxed for 2 h in a mixture of dimethylformamide (2 ml) and methyl iodide (0·2 ml). The solution was evaporated to dryness; the residue was dissolved in dichloromethane (5 ml) and washed with 10% sodium hydroxide solution. Removal of the solvent left 2,4-diisopropyl-1-methylimidazole (IVk) (30 mg), b.p. 120—130° (bath) at 15 mmHg.

(b) *With dimethyl sulphate*. A mixture of compound (IIk) (100 mg), benzene (10 ml), and pure dimethyl sulphate (0·1 ml) was refluxed for 3 h, then washed three times with 10% sodium hydroxide solution and three times with water, dried, and distilled, yielding 2,4-di-isopropyl-1-methylimidazole (IVk) (10 mg), b.p. 120—130° (bath) at 15 mmHg.

Methylation of Compound (Ik) *with Dimethyl Sulphate*.—A mixture of compound (Ik) (200 mg), dimethyl sulphate (0·2 ml), and benzene (20 ml) was treated in a similar way to (IIk), and the crude product was treated with Raney nickel to give (IVk) (30 mg).

Methylation of Compound (VI).—(a) *With dimethyl sulphate*. Application of the foregoing treatment to a mixture of compound (VI) (200 mg), dimethyl sulphate (0·2 ml), and benzene (20 ml) yielded (IVk) (25 mg).

(b) *With methyl iodide–potassium carbonate*. A mixture of compound (VI) (532 mg), methyl iodide (1·0 g), potassium carbonate (0·5 g), and methanol (10 ml) was refluxed for 3 h. The solvent was evaporated off and the residue was refluxed with light petroleum. Undissolved potassium carbonate was filtered off and distillation of the filtrate left a crystalline residue (391 mg), which was recrystallized from light petroleum (Found: C, 62·7; H, 7·15; N, 9·05. Calc. for $C_{16}H_{22}N_2O_2S$: C, 62·75; H, 7·25; N, 9·15%). This methylated product (318 mg) was refluxed in a mixture of Raney nickel and ethanol (10 ml) in the usual way. The catalyst was filtered off and the filtrate was evaporated to yield compounds (IVk) and (Vk) (93 : 7).

Butylation of Compound (Ij) *with n-Butyl Iodide–Potassium Carbonate*.—A mixture of compound (Ij) (1·0 g), n-butyl iodide (3·0 g), potassium carbonate (1·0 g), and methanol (20 ml) was refluxed for 8 h. The methanol and excess of n-butyl iodide were distilled off under reduced pressure. The residue was refluxed with light petroleum and the remaining potassium carbonate was filtered off. The solvent was distilled off to leave the alkylated product (118 mg), b.p. 190—196° (bath) at 3 mmHg. This was treated with Raney nickel by the standard procedure to give 1-n-butyl-2-isopropyl-4-n-propylimidazole (VII) (71 mg), b.p. 115—118° (bath) at 3 mmHg $\tau(CCl_4)$ 3·70 (1H, t, J 0·9 Hz, H-5) and 6·27 (2H, t, J 7·5 Hz, N·CH_2Pr).

Butylation of Compound (IIj) *with n-Butyl Iodide–Potassium Carbonate*.—A mixture of compound (IIj) (190 mg), n-butyl iodide (0·7 g), potassium carbonate (1·0 g), and methanol (4·0 ml) was set aside at room temperature for 30 days. The solvent and excess of n-butyl iodide were evaporated off under reduced pressure. The residue was mixed with water and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated, leaving a large portion of unchanged (IIj) and a trace of compound (VII).

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