410. *The Thermal Condensation of Imidazoles with Carbonyl Compounds.*

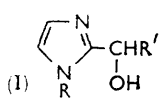
By A. M. Roe.

1-Substituted 2-1′-hydroxy-alkyl- and -aryl-imidazoles (I) are obtained by thermal condensation of 1-methyl-, 1-benzyl-, and 1-methoxymethyl-imidazole with aldehydes. These, and other, alcohols are also obtained from the lithium derivative of the imidazole. 2-Acetylimidazole has been prepared and characterised. 1,4-Diketones react with imidazole to give imidazo[1,2-*a*]-pyridines (II).

The reactivity of derivatives of imidazole towards formaldehyde and chloral has been known for more than half a century.[1,2] Thus, formaldehyde with 1-methyl- or 1-benzyl-imidazole gives the derived 2-hydroxymethylimidazole.[3] There is no record of simple condensation of an imidazole with other carbonyl compounds. This investigation started with a study of the reaction between 1-substituted imidazoles and benzaldehyde.

1-Methylimidazole has been prepared by many methods in yields ranging from poor to 69%;[4] a discussion of the difficulty of preparing 1-alkylimidazoles in good yield is given by Häring.[4] Jocelyn[5] claimed to have prepared 1-methylimidazole in 75% yield, but recalculation shows this to have been 64%; in our hands it is variable by his method. This compound has now been conveniently prepared (72%) from methyl iodide and the sodium salt of imidazole in liquid ammonia.

Heating 1-methylimidazole at temperatures between 130° and 155° for 17—22 hours with either 1 or 3 mol. of benzaldehyde under oxygen-free nitrogen, gave the alcohol (I; R = Me, R′ = Ph) in 35—40% yield, together with benzoin (6% based on benzaldehyde) and an unidentified compound, $C_{18}H_{18}N_2O_2$ (<1%), which may be a condensation product of 1-methylimidazole with benzoin or a trisubstituted imidazole. The occurrence of benzoin (and, when *p*-anisaldehyde was used instead of benzaldehyde, *p*-anisil) is interesting in view of the previously described catalytic action of 1,3,4-trimethylimidazolium iodide in promoting the benzoin condensation.[6]


(I)

1-Methylimidazole has also been successfully condensed with n-heptaldehyde and isobutyraldehyde (for conditions and yields see Table 1); in the former case much αβ-unsaturated aldehyde was produced by self-condensation of the aldehyde.

The formulation of all these products, which were isolated as bases or crystalline hydrochlorides, as 1-(1-methylimidazol-2-yl)-alcohols (I; R = Me) is based on the known orientation of the 2-hydroxymethyl compound and the independent synthesis of these and other compounds (see below).

In order to provide a possible route to alcohols unsubtituted on the nitrogen atoms (I; R = H), these reactions were studied with 1-benzylimidazole, which was prepared in 75% yield, in a similar manner to 1-methylimidazole. This compound has previously been converted into its 2-hydroxymethyl derivative[7] which was debenzylated by the action of sodium in liquid ammonia.[7] It can be seen (Table 1) that the yields of alcohols obtained from this base seem to bear no relation to those obtained with 1-methylimidazole.

A further series of thermal condensations has been performed on 1-methoxymethylimidazole (the conditions and products being listed in Table 1). 1-Methoxymethylimidazole is readily prepared (81%) and it was hoped that the methoxymethyl group

[1] Windaus, *Ber.*, 1909, **43**, 758.
[2] Grindley and Pyman, *J.*, 1927, 3128.
[3] Hofmann, "Imidazole and its Derivatives," Interscience Publ., Inc., New York, 1953, Part I, p. 99.
[4] Häring, *Helv. Chim. Acta*, 1959, **42**, 1845.
[5] Jocelyn, *J.*, 1957, 3305.
[6] Ukai, Dokawa, and Tsubokawa, *J. Pharm. Soc. Japan*, 1944, **64**, No. 7A, 3.
[7] Jones, *J. Amer. Chem. Soc.*, 1949, **71**, 383.

would be cleaved by acid (cf. the cleavage of the corresponding carbazole derivative [8]); however, the base itself and the derived alcohols are stable to prolonged boiling in 6N-hydrochloric acid.

The optimum conditions for these thermal condensations have not been sought, and in some cases the yield seemed to be critically dependent on the temperature. However,

TABLE 1.

Conditions of thermal condensation and yield of the alcohols (I).

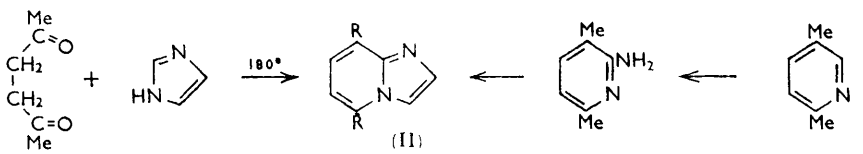
	R = Me		R = CH_2Ph		R = $MeO{\cdot}CH_2$	
R′	Conditions	Yield (%)	Conditions	Yield (%)	Conditions	Yield (%)
H	*	23	115°/17 hr.†	61	125°/20 hr.†	45
n-C_6H_{13}	148°/18 hr.	35	150°/19 hr.	12	152°/15 hr.	40
Pr^i	148°/18 hr.	24	145°/16 hr.	42 ‡	158°/19 hr.	46
			155°/40 hr.	45		
Bu^t	142°/17 hr.	0	151—163°/65 hr.	15	§	
Ph	135°/22 hr.	36	152°/16 hr.	15	150°/17 hr.	0
	155°/17 hr.	40				
p-$MeO{\cdot}C_6H_4$	145°/17 hr.	12	§		§	

* Conditions used by Jocelyn.[5] † 40% Aq. formaldehyde; cf. Jones.[7] ‡ 88% based on 1-benzylimidazole not recovered. § Reaction not tried.

an extended time of heating did not appear to increase the yield of condensation product significantly (see Table 1). No products could be isolated from these 1-substituted imidazoles and aqueous or anhydrous acetaldehyde, chloral hydrate, cyclohexanone, *p*-dimethylaminobenzaldehyde, *p*-nitrobenzaldehyde, or hexane-2,5-dione.

Alternative methods of condensation have been explored. In no case could an acid-catalysed reaction be effected; but the reaction between 1-methylimidazole and benzaldehyde was effected (9% yield) by 24 hours' boiling in xylene.

Some of these alcohols and a number of others have been synthesised by reaction of the lithium derivative of the imidazole with the appropriate carbonyl compound, a method described by Shirley and Alley.[9] This is the preferred synthetic process since ketones, *p*-dimethylaminobenzaldehyde, and heterocyclic aldehydes react giving fair yields. The reaction of the lithium derivative of 1-benzylimidazole and ethyl formate has given the di-imidazolylmethanol. Table 2 gives the alcohols prepared by this method.



Advantage was taken of the availability of 1-(1-benzylimidazol-2-yl)ethanol (I; R = CH_2Ph, R′ = Me) to prepare the debenzylated compound by the action of sodium in liquid ammonia, the product being obtained in quantitative yield. Oxidation of this product with chromium trioxide–pyridine gave what is considered to be authentic 2-acetylimidazole (m. p. 137°), in contradistinction to the poorly authenticated product (m. p. 80°) that Oddo and Ingraffia [10] prepared by the action of acetyl chloride on the Grignard derivative of imidazole.

For the condensation of imidazole itself with carbonyl compounds the only reagents that yielded tractable products were 1,4-dicarbonyl compounds. Hexane-2,5-dione and imidazole gave 5,8-dimethylimidazo[1,2-*a*]pyridine (II; R = Me), this structure being based on the properties and the synthesis by a modification [11] of the conventional

[8] O'Brien and Smith, *J.*, 1960, 4609.
[9] Shirley and Alley, *J. Amer. Chem. Soc.*, 1957, **79**, 4922.
[10] Oddo and Ingraffia, *Gazzetta*, 1931, **61**, 446.
[11] Mosby, " Heterocyclic Systems with Bridgehead Nitrogen Atoms," Interscience Publ., Inc., New York, 1961, Part I, p. 461.

Tschitschibabin method. 2,5-Lutidine was heated with 1·5 mol. of sodamide in refluxing xylene, to give 2-amino-3,6-dimethylpyridine, whose structure was confirmed when the action of nitrous acid furnished 3,6-dimethyl-2-pyridone. Cyclisation with bromoacetaldehyde gave the base (II; R = Me).

In one experiment, replacement of the hexane-2,5-dione by 2,5-diethoxytetrahydrofuran gave the known parent base (II; R = H); repetition of this experiment gave a base, $C_9H_{14}N_2O_2$, of undetermined constitution which is probably 1-(5-ethoxytetrahydro-2-furyl)imidazole, since it gives no colour in the Pauly test for imidazoles unsubstituted on the nitrogen atom; its apparent stability to acid is surprising but may be related to the fact that 1-methoxymethylimidazole is also not cleaved by acid (see above).

Experimental

1-Methylimidazole.—Imidazole (27·2 g.) was added to a solution of sodium (10 g.) in liquid ammonia (600 ml.) containing a crystal of ferric nitrate. Methyl iodide (66 g.) was then added during 15 min. with stirring which was continued for 1 hr. The residue left after evaporation of the ammonia was dissolved in water (300 ml.) and continuously extracted with chloroform. Distillation of the extract gave 1-methylimidazole (23·7 g., 72%), b. p. 97°/18 mm.

1-Benzylimidazole.—Imidazole (27·2 g.) was added to a solution of sodium (10 g.) in liquid ammonia (600 ml.) containing a crystal of ferric nitrate. Benzyl bromide (70 g.) was slowly added to the stirred solution which was then left to evaporate. The residue was extracted with chloroform and the extract distilled, to give 1-benzylimidazole (47·3 g., 75%), b. p. 112—117°/0·5 mm. This base separated from light petroleum (b. p. 40—60°) as needles, m. p. 70—71·5°.

1-Methoxymethylimidazole.—A stirred suspension of imidazole (60 g., 0·83 mole) in dry benzene (200 ml.) was treated with chlorodimethyl ether (34·3 g., 0·425 mole) in dry benzene (100 ml.). The mixture became warm and the imidazole was gradually replaced by a pale yellow oil. Stirring was continued for 2 hr. and then the mixture was distilled. The fraction of b. p. 64—110°/0·1 mm. was redistilled, to give pure *1-methoxymethylimidazole* (37·5 g., 81%), b. p. 111—112°/23 mm., n_D^{23} 1·4847, $\nu_{max.}$ (in $CHCl_3$) 1505, 1114, 1103, 1072, and 667 cm.$^{-1}$ (Found: C, 53·3; H, 7·1; N, 24·7. $C_5H_8N_2O$ requires C, 53·6; H, 7·2; N, 25·0%). The *picrate* (needles from ethanol) had m. p. 152° (Found: C, 38·6; H, 2·4; N, 20·2. $C_{11}H_{11}N_5O_8$ requires C, 38·7; H, 3·25; N, 20·5%). The *methopicrate* (needles from ethyl acetate) had m. p. 89—90° (Found: C, 40·8; H, 3·7; N, 19·7. $C_{12}H_{13}N_5O_8$ requires C, 40·6; H, 3·7; N, 19·7%).

Table 2.

Alcohols (I) (or their hydrochlorides) prepared but not described in text.

			Yield		Found (%)				Required (%)		
R′	R	M. p.	(%)	Method *	C	H	N	Formula	C	H	N
n-C_6H_{13}	Me	116—117°	35	T	56·8	9·1	12·0	$C_{11}H_{21}ClN_2O$ §	56·8	9·1	12·0
			41	L							
Pr^i	Me	78·5—79·5	24	T	62·2	9·3	18·4	$C_8H_{14}N_2O$	62·3	9·15	18·2
H	CH_2Ph	165—166·5 †	61	T				$C_{11}H_{13}ClN_2O$			
n-C_6H_{13}	CH_2Ph	113—114	12	T	74·9	8·9	10·4	$C_{17}H_{24}N_2O$	74·95	8·9	10·3
Bu^t	CH_2Ph	112·5—114	15	T	73·6	8·3	11·5	$C_{15}H_{20}N_2O$	73·7	8·25	11·5
Ph	CH_2Ph	110—111·5	15	T	77·2	6·1	10·6	$C_{17}H_{16}ClN_2O$	77·2	6·1	10·6
		190—193 ‡	48	L	68·0	5·7	9·3	$C_{17}H_{17}ClN_2O$ ¶	67·9	5·7	9·3
H	$MeO·CH_2$	82—84	75	T	50·8	7·15	19·7	$C_6H_{10}N_2O_2$	50·7	7·1	19·7
Pr^i	$MeO·CH_2$	108·5	46	T	58·75	8·8	15·3	$C_9H_{16}N_2O_2$	58·7	8·8	15·2
Ph	$MeO·CH_2$	148	45	L	56·6	5·8	11·0	$C_{12}H_{15}ClN_2O_2$ **	56·6	5·9	11·0
n-C_6H_{13}	$MeO·CH_2$	73—74	40	T	63·6	9·8	12·3	$C_{12}H_{22}N_2O_2$	63·7	9·8	12·4
3,4-$(MeO)_2C_6H_3$	Me	196·5—198 ‡	23	L	54·7	6·1	9·9	$C_{13}H_{17}ClN_2O_3$ ††	54·8	6·0	9·8
CH_2Ph	Me	157—160	44	L	71·15	7·05	13·9	$C_{12}H_{14}N_2O$	71·3	7·0	13·85
p-$Me_2N·C_6H_4$	Me	142—143	48	L	67·4	7·5	18·0	$C_{13}H_{17}N_3O$	67·5	7·4	18·2
Me	CH_2Ph	105·5—106·5	22	L	71·1	7·3	13·8	$C_{12}H_{14}N_2O$	71·3	7·0	13·85
2-C_5H_4N	Me	222—223 ‡	48	L	45·3	5·3	15·8	$C_{10}H_{13}Cl_2N_3O$ ‡‡	45·2	5·1	15.8

* T = Thermal condensation; L = reaction *via* lithium derivative. † Jones [7] records m. p. 161·5—162°. ‡ With decomp. ‡‡ $+0·2H_2O$. Found: Cl, § 15·1, ¶ 11·7, ** 13·5, †† 12·7, ‡‡ 26·5. Reqd.: Cl, § 15·2, ¶ 11·8. ** 13·9, †† 12·45, ‡‡ 26·7.

Thermal Condensation of 1-*Substituted Imidazoles with Aldehydes.*—Three examples only of this reaction will be described in detail.

(*a*) *Benzaldehyde.* 1-Methylimidazole (2·13 g., 0·026 mole) and freshly distilled benzaldehyde (8·45 g., 0·08 mole) were sealed under nitrogen (scrubbed with Fieser's solution and dried) and heated at 135° for 22 hr. The colourless mixture was dissolved in benzene (100 ml.) and extracted with dilute hydrochloric acid (3 × 30 ml.). The extract was basified with 50% aqueous sodium hydroxide, giving a gelatinous solid which was extracted into ethyl acetate. The dried (Na_2SO_4) extract was evaporated to a semi-solid oil (2·34 g.) which was dissolved in warm ether, filtered, and allowed to cool, giving α-(1-*methylimidazol-2-yl*)*benzyl alcohol* as needles (1·79 g., 36%), m. p. 108·5—110·5°. Crystallisation from acetone, in which a minor component is insoluble (see below), raised the m. p. to 113° (Found: C, 70·2; H, 6·4; N, 14·85. $C_{11}H_{12}N_2O$ requires C, 70·2; H, 6·4; N, 14·9%). The *hydrochloride* (plates from ethanol) sintered and became pink at 190° and decomposed at 208—210° (Found: C, 58·9; H, 5·9; N, 12·4; Cl, 15·7. $C_{11}H_{13}ClN_2O$ requires C, 58·8; H, 5·8; N, 12·5; Cl, 15·8%). The *methopicrate* (needles from ethanol) had m. p. 178—180° (decomp.) (Found: C, 50·4; H, 3·9; N, 16·15. $C_{18}H_{17}N_5O_8$ requires C, 50·1; H, 4·0; N, 16·2%). The minor *component*, which was insoluble in acetone, separated from ethyl acetate in needles (0·05 g.), m. p. 236° (Found: C, 73·2; H, 6·1; N, 9·6. $C_{18}H_{18}N_2O_2$ requires C, 73·4; H, 6·2; N, 9·5%).

In another experiment under the same conditions, the reaction mixture, dissolved in ethanol and dilute hydrochloric acid, was steam-distilled. The cooled residue contained a pale yellow solid which after crystallisation from ethanol gave needles, m. p. 134°, undepressed on admixture with benzoin.

(*b*) p-*Methoxybenzaldehyde.* 1-Methylimidazole (2·13 g., 0·026 mole) and *p*-methoxybenzaldehyde (3·55 g., 0·026 mole) were heated in a sealed tube under oxygen-free nitrogen at 145° for 17 hr. The mixture was partitioned between chloroform and dilute hydrochloric acid, and the aqueous layer was filtered, basified, and extracted with chloroform. The dried (Na_2SO_4) extract was evaporated to a brown oil (2·50 g.) which was dissolved in ethanolic hydrogen chloride. Addition of ether gave 4-*methoxy*-α-(1-*methylimidazol-2-yl*)*benzyl alcohol hydrochloride* (0·76 g., 12%), m. p. 188—191°; after recrystallisation from ethanol this had m. p. 191—194° (decomp.) (Found: C, 56·6; H, 6·1; N, 11·2; Cl, 14·1. $C_{12}H_{15}ClN_2O_2$ requires C, 56·6; H, 5·9; N, 11·0; Cl, 13·9%). The original chloroform solution was evaporated. The residue, dissolved in ethanol, was treated with saturated aqueous sodium hydrogen sulphite solution. After cooling, the solid was filtered off and washed with ethanol, and the filtrate and washings were evaporated; the resulting anisil, crystallised from carbon tetrachloride, had m. p. and mixed m. p. 131—132·5°, with the correct infrared spectrum.

(*c*) *Isobutyraldehyde.* 1-Benzylimidazole (2·36 g.) and isobutyraldehyde (3·2 g.) were sealed under pure nitrogen and heated at 145° for 16 hr. The colourless mixture was dissolved in chloroform and extracted with dilute hydrochloric acid. The extract was heated (to remove chloroform) and then basified while chilled in ice and water. The precipitated 1-(1-*benzylimidazol-2-yl*)-2-*methylpropan*-1-*ol* (1·44 g.), m. p. 133—137°, was collected; when crystallised from ethyl acetate, it had m. p. 136·5—137·5° (Found: C, 72·8; H, 7·8; N, 11·6. $C_{14}H_{18}N_2O$ requires C, 73·0; H, 7·9; N, 12·2%). The filtrate from the alcohol was extracted with chloroform, and the dried (Na_2SO_4) extract was evaporated, to give 1-benzylimidazole (1·24 g.), m. p. 65—68·5°, raised to 68—70° on admixture with the pure base.

Reaction of the Lithium Derivatives of 1-*Substituted Imidazoles and Carbonyl Compounds.*—Ethereal n-butyl-lithium was prepared [12] and stored at 0°; it was standardised [12] before use. Three typical preparations will be described.

1-(1-*Methylimidazol-2-yl*)*cyclohexanol.*—1-Methylimidazole (1·0 g.) in dry ether (40 ml.) was treated with ethereal 1·3M-n-butyl-lithium (12 ml.) and after being stirred at room temperature for 1 hr. the solution was cooled to 0°; cyclohexanone (1·3 g.) was added, giving an immediate white precipitate. The mixture was allowed to reach room temperature and kept for 3 hr. Water (15 ml.), followed by dilute hydrochloric acid (15 ml.), was added; the aqueous layer was separated and basified, and the precipitated solid was collected and crystallised from slightly aqueous ethanol, to give the *cyclohexanol* as needles (1·22 g., 56%), m. p. 177—178° (Found: C, 66·7; H, 9·0; N, 15·6. $C_{10}H_{16}N_2O$ requires C, 66·6; H, 8·95; N, 15·5%). The *hydrochloride*, crystallised from ethanol–ether, had m. p. 199·5° (Found: C, 55·2; H, 8·0; N, 13·0; Cl, 16·2. $C_{10}H_{17}ClN_2O$ requires C, 55·4; H, 7·9; N, 12·9; Cl, 16·4%).

[12] Gilman and Morton, *Organic Reactions*, 1954, **8**, 285.

α-(1-*Methylimidazol-2-yl*)-α-3′-*pyridylmethanol*.—1-Methylimidazole (1·09 g.) in dry ether (40 ml.) was stirred with ethereal 1·1M-n-butyl-lithium (17 ml.) for 2 hr. 3-Formylpyridine (1·47 g.) in dry ether (10 ml.) was added and the mixture stirred for 3 hr. Addition of water gave two layers; the ethereal layer was separated and the aqueous layer continuously extracted with warm chloroform to remove a dark brown oil (1·76 g.), from which the *dihydrochloride hemihydrate* was isolated; crystallised from methanol and ether this (1·17 g., 33%) had m. p. 222° (Found: C, 44·6; H, 5·6; N, 15·7; Cl, 26·3. $C_{10}H_{13}Cl_2N_3O,0{\cdot}5H_2O$ requires C, 44·3; H, 5·2; N, 15·5; Cl, 26·15%).

Di-(1-*benzylimidazol-2-yl*)*methanol*.—Ethereal 1·2M-n-butyl-lithium (40 ml.) was added to a stirred suspension of 1-benzylimidazole (5·52 g.) in dry ether (80 ml.) at 0°. After 2 hr. at 0° the dark red solution was treated with ethyl formate (1·33 g.) in dry ether (50 ml.) and kept at 0° for 2 hr. Addition of water (100 ml.) and dilute hydrochloric acid (75 ml.) gave two layers. The aqueous solution was basified and extracted with chloroform; the oil resulting from the evaporation of the dried (Na_2SO_4) extract crystallised from benzene, to give the *product* (1·30 g., 22%), m. p. 176—177° (Found: C, 73·0; H, 5·8; N, 16·1. $C_{21}H_{20}N_4O$ requires C, 73·2; H, 5·85; N, 16·3%).

1-*Imidazol-2′-ylethanol*.—1-(1-Benzylimidazol-2-yl)ethanol (3·12 g.) was stirred in liquid ammonia (200 ml.) while small pieces of sodium (~0·8 g.) were added until the solution remained blue for 10 min. Ammonium chloride (3·5 g.) was added and the solvent was allowed to evaporate. The residue, dissolved in water (80 ml.), was continuously extracted with ethyl acetate. The extract was concentrated and filtered hot, needles of 1-*imidazol-2′-ylethanol*, m. p. 134—136°, separating (Found: C, 53·6; H, 7·3; N, 25·1. $C_5H_8N_2O$ requires C, 53·6; H, 7·2; N, 25·0%).

2-*Acetylimidazole*.—The foregoing secondary alcohol (0·40 g.) in pyridine (5 ml.) was added to cold chromium trioxide (0·70 g.) in pyridine (7 ml.) and kept at 0—5° for 0·5 hr. After 48 hr. at room temperature the mixture was diluted with water and extracted with warm chloroform for several hours. The dried (Na_2SO_4) extract was evaporated *in vacuo* at 50°. The residue was boiled with successive portions of light petroleum (b. p. 80—100°), which, when concentrated, gave the *ketone* (0·091 g.) as needles, m. p. 135—137·5° (Found, on sample sublimed at 45—60°/0·2 mm.: C, 54·8; H, 5·6; N, 25·5. $C_5H_6N_2O$ requires C, 54·5; H, 5·5; N, 25·4%), $\nu_{max.}$ (KBr) 3160, 1684, 1673, and 1397 cm.$^{-1}$. The *picrate*, needles from ethanol, had m. p. 224—226° (decomp.) (Found: C, 38·9; H, 2·7; N, 20·8. $C_{11}H_9N_5O_8$ requires C, 38·9; H, 2·7; N, 20·65%).

5,8-*Dimethylimidazo*[1,2-*a*]*pyridine*.—(*a*) Imidazole (12·0 g.) and hexane-2,5-dione (42·5 g.) were heated under pure nitrogen in sealed tubes at 180° for 15 hr. The dark liquid was collected in chloroform and carefully fractionated, to give a new *base* (14·1 g.), b. p. 91—93°/0·7 mm., $\nu_{max.}$ (liquid film) 2920, 1635, 1512, and 1327 cm.$^{-1}$, $\lambda_{max.}$ (hexane) 223 mμ (log ε 4·27), 227 (4·24), inflexion at 273 (3·33), 282 (3·40), 294 (3·25), 305 (3·23), and 319 (3·01). The *perchlorate*, m. p. 119—120·5°, crystallised from butan-1-ol (Found: C, 43·8; H, 4·5; N, 11·4; Cl, 14·5. $C_9H_{11}ClN_2O_4$ requires C, 43·8; H, 4·5; N, 11·4; Cl, 14·4%). The *picrate*, m. p. 216—218° (decomp.), crystallised from acetone (Found: C, 48·4; H, 3·5; N, 18·65. $C_{15}H_{13}N_5O_7$ requires C, 48·0; H, 3·5; N, 18·7%). The *methiodide*, m. p. 201—202°, crystallised from ethanol (Found: C, 41·8; H, 4·3; N, 9·7; I, 44·3. $C_{10}H_{13}IN_2$ requires C, 41·7; H, 4·55; N, 9·7; I, 44·0%).

(*b*) Bromoacetaldehyde diethyl acetal (4·33 g.) in dioxan (16 ml.) and water (5 ml.) containing a few drops of concentrated hydrochloric acid was heated under reflux for 0·5 hr. Solid sodium hydrogen carbonate (3·70 g.) was added to the cooled solution, followed by 2-amino-3,6-dimethylpyridine (2·44 g.) in dioxan (10 ml.) and water (6 ml.). The mixture was boiled under reflux for 22 hr., cooled, poured into water, and made acidic with hydrochloric acid. After extraction with ether, basification gave a dark brown oil which was collected in chloroform and passed down a silica gel column to give a pale mobile liquid (1·21 g.), which had an infrared spectrum identical with that of the base prepared as above. The perchlorate and picrate were identical with the previous specimens.

5,6,7,8-*Tetrahydro*-5,8-*dimethylimidazo*[1,2-*a*]*pyridine*.—The foregoing base (0·5 g.) and platinum oxide catalyst (0·1 g.) in ethanol (25 ml.) containing concentrated hydrochloric acid (2 ml.) were shaken under hydrogen. When uptake of hydrogen (2 mol.) ceased, the filtered solution was evaporated to a hygroscopic oil which was treated with dilute sodium hydroxide. Extraction with chloroform and evaporation of the dried (Na_2SO_4) extract gave an oil (0·5 g.),

from which was prepared the *picrate* (needles from ethanol), m. p. 181·5—184° (Found: C, 47·6; H, 4·7; N, 18·25. $C_{15}H_{17}N_5O_7$ requires C, 47·5; H, 4·5; N, 18·5%). The *hydrogen oxalate* (rhombs from propan-1-ol) had m. p. 121—122° (Found: C, 55·1; H, 6·8; N, 11·55. $C_{11}H_{16}N_2O_4$ requires C, 55·0; H, 6·7; N, 11·7%).

2-*Amino*-3,6-*dimethylpyridine*.—Sodamide, from sodium (23·1 g.), was prepared in liquid ammonia. The solvent was slowly displaced by addition of dry xylene (150 ml.), followed by 2,5-lutidine (71·3 g., m. p. *ca.* −25°, obtained from L. Light & Co. Ltd., and having a liquid-film infrared spectrum in accord with that of the purified material [13]) in dry xylene (100 ml.). The mixture was then heated under reflux while protected from moisture for 6 hr. The black product was hydrolysed at 0° with water (250 ml.), followed by concentrated hydrochloric acid (125 ml.). The xylene was separated and washed twice with dilute hydrochloric acid; the combined acidic solutions were washed with benzene and basified. The resulting black oil was collected in chloroform, dried (Na_2SO_4), and fractionated to give unchanged 2,5-lutidine (15·8 g.), 2-amino-3,6-dimethylpyridine (16·8 g.), b. p. 119—121°/20 mm., m. p. 39—46°, an intermediate fraction (4·6 g.), and a deep red viscous liquid (2·6 g.), b. p. 155°/10^{-2} mm., which slowly solidified.

2-*Amino*-3,6-*dimethylpyridine*, m. p. 49·5—51°, crystallised in needles from light petroleum (b. p. 60—80°) (Found: C, 68·4; H, 8·1; N, 22·9. $C_7H_{10}N_2$ requires C, 68·8; H, 8·25; N, 22·9%). The *picrate*, m. p. 227—228° (decomp.), crystallised in needles from acetone (Found: C, 44·3; H, 4·2; N, 19·8. $C_{13}H_{13}N_5O_7$ requires C, 44·45; H, 3·7; N, 19·9%). Treatment of the base with nitrous acid and sublimation of the neutralised residue gave 3,6-dimethyl-2-pyridone, m. p. 137—138°, which gave a blood red colour with aqueous ferric chloride (Errera [14] records m. p. 138—139°).

Crystallisation of the fraction, b. p. 155°/10^{-2} mm., from benzene gave a colourless substance, m. p. 137·5—138·5° (Found: C, 74·0; H, 7·5; N, 18·5. $C_{14}H_{17}N_3$ requires C, 74·0; H, 7·5; N, 18·5%), which is considered to be *di*-(3,6-*dimethyl*-2-*pyridyl*)*amine*.

Imidazo[1,2-*a*]*pyridine*.—(*a*) Imidazole (7·0 g.) and 2,5-diethoxytetrahydrofuran (45·6 g.) were heated under pure nitrogen in sealed tubes at 166—179° for 14 hr. The resulting black solid was digested with hot dilute hydrochloric acid and chloroform, the acid-soluble extract was basified, and the base, collected in chloroform, was distilled (3·85 g.; b. p. 76—148°/0·35 mm.). The base was purified as the picrate (needles from ethanol), m. p. 203—205° (Bower [15] gives m. p. 205°),and converted into its methiodide (needles from propan-1-ol), m. p. 206—208° (Bower [15] gives m. p. 207°).

(*b*) Bromoacetaldehyde diethyl acetal (10·80 g.) in dioxan (30 ml.) and water (20 ml.) containing a few drops of concentrated hydrochloric acid was boiled for 0·5 hr. Solid sodium hydrogen carbonate (9·25 g.) was added to the cooled solution, followed by 2-aminopyridine (4·70 g.) in dioxan (15 ml.) and water (10 ml.). The mixture was boiled under reflux for 22 hr., cooled, acidified to Congo Red, and extracted with ether. The aqueous solution was made strongly basic and continuously extracted with warm chloroform. The resulting base (4·99 g., 85%) had b. p. 88—90°/0·7 mm. (Bower [15] gives b. p. 109°/2 mm.). The picrate and methiodide were identical with those obtained as above. The *perchlorate* prepared in, and crystallised from, ethanol, had m. p. 241—243·5° (decomp.) (Found: C, 38·2; H, 3·2; N, 12·7; Cl, 16·4. $C_7H_7ClN_2O_4$ requires C, 38·5; H, 3·2; N, 12·8; Cl, 16·2%).

Repetition of experiment (*a*) above but heating the reagents at 147° for 16 hr. gave a solid basic product which was passed down a silica gel column in chloroform to yield a *substance* [colourless rhombs from benzene–light petroleum (b. p. 60—80°)], m. p. 134—137°, $\nu_{max.}$ (KBr) 1063 $cm.^{-1}$ (Found: C, 59·3; H, 7·7; N, 15·2. $C_9H_{14}N_2O_2$ requires C, 59·3; H, 7·7; N, 15·4%). The *picrate* had m. p. 120—132° after several crystallisations from ethanol (Found: C, 43·7; H, 4·5; N, 16·65. $C_{15}H_{17}N_5O_9$ requires C, 43·8; H, 4·2; N, 17·0%).

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SMITH KLINE AND FRENCH RESEARCH INSTITUTE,
WELWYN GARDEN CITY, HERTS.

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[13] Coulson, Cox, Herington, and Martin, *J.*, 1959, 1934.
[14] Errera, *Ber.*, 1901, **34**, 3691.
[15] Bower, *J.*, 1957, 4510.