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Imidazoles. II.¹⁾ A General Synthesis for 1-Hydroxyimidazoles

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The reaction of α -dione monoximes with aldehydes and ammonia affords a general and facile synthetic route to 1-hydroxyimidazoles. By selection of the starting materials substituents can be readily introduced into the 2,4 and/or 5 positions of the imidazole ring which is formed via the intermediacy of a gem-aminoalcohol. The reactions of the N-hydroxyl function are discussed.

In a study of cellulosic fiber-polymer interactions^{4,5}) we have been concerned with the synthesis of imidazoles⁶⁻⁹) and other polyaza heterocycles suitable for the attachment of vinylic moieties having differing reactivity ratios.¹⁰) Thus, although 4(5)-vinylimidazole has been described,¹¹⁻¹⁵⁾ the procedure is not amenable to facile variation and this alkene does not readily copolymerize with a wide range of monomers.¹³⁾ Our attention was thus directed to the fact that almost exactly half a century ago Diels discovered¹⁵) that when aldehydes (RCHO) and butane-2,3-dione monoxime

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(I) are shaken with aqueous ammonia, a clan of compounds is formed by the elimination of two moles of water. Their reductive conversion into trisubstituted imidazoles (III) and their reversible hydrolysis to products considered to be the diols (IV) led¹⁶) to their formulation as II.



Although the synthesis of the somewhat labile oxaziridine ring system has been achieved^{17,18}) by several, usually oxidative, procedures, its generally limited stability in alkaline solutions and its apparent ease of formation in this alkaline condensation suggested that a re-examination of this group of products was merited.

Repetition of the prescribed procedure smoothly afforded II in good yield. Examination of this compound then disclosed (for R=Ph) that IV is a simple hydrate of II and that the transformations

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of IV into II and II into IV can readily be effected by crystallization from anhydrous and aqueous solvents respectively. The transition $IV \rightarrow II$ can also be realized by melting. The representational inadequacies of the general formula II were further underscored by the ultraviolet absorption spectrum of the congener (II, R=Me) originating from acetaldehyde which exhibited an absorption maxi-This is indicative mum at 2240 Å ($\varepsilon = 8800$). of the di-unsaturation of an imidazole ring and further clarification of the alleged structure II (with R=Me) resulted from a scrutiny of its nuclear magnetic resonance spectrum in chloroform solution. This contained three singlets ($\tau =$ 8.02, 7.77 and -3.33 ppm) corresponding to a pair of closely similar methyl groups, a single different methyl group and a very polar proton. These facts are in accord with a general hydroxylamine formulation (VI) and its hydrate as the corrected versions of the structure of these condensation products previously represented as II and IV respectively. A more recently suggested formulation of these products as N-oxides (V) and their hydrates¹⁹⁾ could be discounted in favor of the hydroxylamine representation because the condensation product, with R=phenyl, is amphoteric (pK_A) 9.41, pK_B 9.36) and because its derived benzoate forms a well defined hydrochloride salt which of course requires the presence of a basic center. Final definitive chemical evidence eliminating the *N*-oxide alternative (V) was secured by replacing butane-2,3-dione monoxime (I) in the condensation reaction with its O-benzoate (VII).20) The product isolated was also a benzoate (VIII) and was identical with that afforded by direct benzoylation of the condensation product originating from butane-2,3dione monoxime itself. The moderate yield of VIII provided by the O-benzoate (VII) can be attributed to the diminution in the nucleophilic character of the oxime nitrogen occasioned by the attached benzoyloxy group.



With structure VI established, many of the previously recorded transformations of these compounds are obviously inadequately formulated and

Table	1.	Reform	ULATED	DERIV	ATIVES	of 1	-
HYDRO	XY-	2-pheny	1-4,5-ы	иетну	LIMIDA	ZOLES	5
	ORI	GINALLY	PREPARE	ED BY	DIELS		

ANC SALOMON¹⁵⁾

Derivatizing reagent	Formula	Reaction product mp °C	Structure
EtOOCNCO	$\mathrm{C_{15}H_{17}N_{3}O_{4}}$	N 80	Ie Me
PhNCO	$C_{18}H_{17}N_3O_2$	M 140	fe Me N N Ph OCONHPh
CH3COCI	$C_{13}H_{15}N_2O_2C$	N 1148 1	fe Me NH Cl- Ph OCOCH ₃
EtNCO	$C_{14}H_{17}N_3O_2$	N 116 1	$ \begin{array}{c} \text{fe} \text{Me} \\ \searrow \\ N N \\ & & \\ $
PhCOCl	$C_{18}H_{17}N_2O_2C$	N 1 162 1	Ie Me N NH Cl- Ph OCOPh

this situation is remedied by the clarifications summarized in Table 1. The evolution of carbon dioxide and the isolation of diphenylurea from the reaction of phenyl isocyanate with IV^{16} is further substantiation of the hydrate structure. It is to be emphasized that the hydrates are the usual reaction products isolated and these can easily be mistaken²⁴ for the parent hydroxylamine.

Another objective of this research was to begin an assessment of the generality and scope of this synthetic route to 1-hydroxyimidazoles, a class of compounds not previously explicitly recognized although the corresponding 1-hydroxybenzimidazoles²¹) are known and noted for their physiological action and the closely related N-oxides have been described.²²⁻²⁶)

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Compound*	Crystalline form**	°C	Yield %	Formula	% Nit Calcd	trogen Found
1-Hydroxy-2,4,5-trimethylimidazole	Light tan needles ^{b)}	6263	77	$C_6H_{10}N_2O$	22.2	22.4
1-Hydroxy-2-ethyl-4,5-dimethylimidazole	White needles ^a)	5353.5	55	$C_7H_{12}N_2O$	20.0	20.3
1-Hydroxy-2-isopropyl- 4,5-dimethylimidazole	White plates ^a)	141-141.5	5 25	$\mathrm{C_8H_{14}N_2O}$	18.1	17.7
1-Hydroxy-2-methoxymethyl- 4,5-dimethylimidazole	White needles ^{c)}	234—236	10	$\mathrm{C_7H_{12}N_2O_2}$	17.9	18.1
1-Hydroxy-2-(1-methyl- <i>n</i> -butyl)- 4,5-dimethylimidazole	White needles ^a)	125—127	25	$C_{10}H_{18}N_{2}O$	15.4	15.0
1-Hydroxy-2-(1-ethyl-1-n-butyl-4-methyl- penta-2,3-dienyl)-4,5-dimethylimidazole	Colorless rhomboids ^{a)}	206—208	8	$C_{17}H_{28}N_2O$	10.1	9.8
1-Hydroxy-2-vinyl-4,5-dimethylimidazole	White needles ^{a)}	90—94	14	$C_7H_{10}N_2O$	20.3	20.5
1-Hydroxy-2-trichloromethyl- 4,5-dimethylimidazole	White needles ^{a,d)}	175—180(d	l) 18	$C_6H_7N_2OCl_3$	12.2	12.1
1-Hydroxy-2-vinyl-4,5-diphenylimidazole	Tan needles ^{c)}	180—184	15	$\mathrm{C_{17}H_{14}N_{2}O}$	10.7	10.6
1-Hydroxy-4,5-diphenylimidazole	White plates ^{a,d)}	210—211	8	$C_{15}H_{12}N_2O$	11.9	12.0
1-Hydroxy-2-(2-ethyl- <i>n</i> -pentyl)- 4,5-diphenylimidazole	White needles ^{e)}	234—235	85	$\mathrm{C_{22}H_{26}N_2O}$	8.4	8.9
1-Hydroxy-2-methyl-4,5-diphenylimidazole	Pinkish white rhomboidse)	247248	20	$\mathrm{C_{16}H_{14}N_{2}O}$	11.2	10.7
$\label{eq:l-Hydroxy-2-phenylphenanthrimidazole} 1-Hydroxy-2-phenylphenanthrimidazole***$	Colorless needles ^{c,e)}	280282	34	$\mathrm{C_{21}H_{14}N_{2}O}$	9.0	8.9

TABLE 2.	Properties	OF	1-HYDROXYIMIDAZOLES
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* The 13 compounds appearing in this Table were similarly prepared and were dehydrated before crystallization from anhydrous solvents.

** Crystallization solvents: a) acetone, b) dioxan, c) ethanol, d) hexane, c) dimethylformamide.

*** The hydrate²⁴⁾ has mp 235–238°C.

Since the formation of these 1-hydroxyimidazoles probably requires the genesis of an aldehydeammonia intermediate as the initial step, a wide variety of aldehydes should be capable of participation in this cyclization with butane-2,3-dione monoxime. This is indeed the case and the properties of the 2-substituted 1-hydroxyimidazoles obtained from various aldehydes are collected in Table 2. The participation of the aldehyde ammonia intermediate was confirmed by the formation of the same 1-hydroxyimidazole (IX) from trichloroacetaldehyde (X) and also directly from 1-amino-2,2,2-trichloroethanol (XI)²⁹⁾ without the use of aqueous ammonia.

$$\begin{array}{ccc} & \underset{\text{CCl}_{3}\text{CHO}}{\text{Me}} & \underset{\text{NH}_{2}}{\text{I}} & \underset{\text{N}}{\overset{\text{N}}{\overset{\text{N}}{\underset{\text{N}}{\underset{\text{N}}{\underset{\text{CCl}_{3}}{\underset{\text{OH}}{\underset{\text{CCl}_{3}}{\underset{\text{OH}}{\underset{\text{CCl}_{3}}{\underset{\text{OH}}{\underset{\text{CCl}_{3}}{\underset{\text{CH}}{\underset{\text{NH}_{2}}{\underset{\text{MH}_{2}}{\underset{\text{NH}_{2}}{\underset{NH}}}{\underset{NH}_{2}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}{\underset{NH}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}{\underset{NH}}{\underset{NH}}{\underset{NH}}{\underset{NH}}{\underset{NH}}{\underset{NH}}{\underset{NH}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}{\underset{NH}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}{\underset{NH}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}}{\underset{NH}}}{\underset{NH}}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}}{\underset{NH}}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}}{\underset{NH}}}{\underset{NH}}{\underset{NH}}}$$

The versatility of this synthetic route to 1hydroxyimidazoles can also be further extended by replacement of the aliphatic α -dione monoxime (I) with the monoximes of aromatic diketones such as benzil or *o*-phenanthraquinone. These variations permit the introduction of polymerizable moieties of various types in positions 2, 4 and 5 of the imidazole ring.

Experimental

General Preparation of 1-Hydroxyimidazoles.

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An equimolecular solution of the aldehyde and the dione monoxime in the minimum amount of ethanol (95%) or dioxan was treated at room temperature with aqueous ammonia (d, 0.88; 80 ml/mol of dione monoxime) when an exotherm was usually noted. The temperature was not allowed to rise above 60°C and the reaction mixture was allowed to stand overnight before collecting and crystallizing the product which had separated.

1-Benzoyloxy-2-phenyl-4,5-dimethylimidazole (VIII). a) A solution of 1-hydroxy-2-phenyl-4,5dimethylimidazole (0.859 g, 3.4 mmol) in dioxan (200 ml) was heated with benzoyl chloride (0.63 g, 5 mmol) at 80—100°C for 10 min. After the addition of a suspension of sodium bicarbonate (0.34 g) in dioxan (100 ml) the reaction mixture was shaken for 10 min, allowed to stand for 5 days at room temperature, warmed to 50°C for 10 min and filtered. The cooled filtrate deposited needles (1.0 g) which were recrystallized from dioxan to give the benzoate (VIII) as needles (0.79 g), mp 163—165°C, which showed an IR absorption maximum at 1730 cm⁻¹.

Found: N, 9.2%. Calcd for C₁₈H₁₆N₂O₂: N, 9.6%.

b) A mixture of benzaldehyde (3.8 g, 0.036 mol) and aqueous ammonia (d, 0.88; 1.8 g, 0.03 mol) in dioxan (200 ml) was treated with butane-2,3-dione monoxime benzoate²⁰) (6.8 g, 0.04 mol, mp 111-113°C) and allowed to stand overnight. The material which had separated was crystallized from dioxan to afford the product as needles (0.5 g), mp 163-165°C, which showed no mp depression when mixed with VIII prepared in a). IR spectra of the two products were superimposable.

Found: N, 9.2%. Calcd for C₁₈H₁₆N₂O₂: N, 9.6%. 1-Hydroxy-2-trichloromethyl-4, 5-dimethylimidazole (IX). a) A solution of trichloroacetaldehyde (2.94g, 0.02 mol) and butane-2,3-dione monoxime (2.02 g, 0.02 mol) in dioxan (6 ml) was treated at room temperature with aqueous ammonia (d, 0.88, 1.6 ml) and allowed to stand overnight. Recrystallization of the separated material from acetone-hexane afforded the product as white needles (0.89 g, 18% yield), mp 175— 180° C (dec).

Found: N, 12.10%. Calcd for: $C_6H_7N_2OCl_3$: N, 12.20%.

b) A solution of 1-amino-2,2,2-trichloroethanol (1.64 g, 0.01 mol) and butane-2,3-dione monoxime (1.01 g, 0.01 mol) in ethanol-dioxan (1 : 1, 4 ml) was allowed to stand overnight, the material which had separated was recrystallized from acetone-hexane to yield

Found: N, 12.15%. Calcd for C₆H₇N₂OCl₃: N, 12.20%.

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