BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 3204—3207 (1969)

Imidazoles. II.[1] A General Synthesis for 1-Hydroxyimidazoles

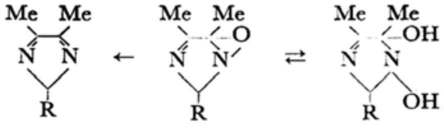
Katsuo AKAGANE,[2] F. J. ALLAN, G. G. ALLAN,[3] T. FRIBERG,
S. Ó MUIRCHEARTAIGH and J. B. THOMSON

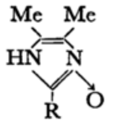
Institute of Forest Products, College of Forest Resources, University of Washington, Seattle, Washington 98105 *U.S.A.*
Chemistry Department, Paisley Technical College, Paisley, Scotland
Department of Chemistry, University College, Dublin, Eire

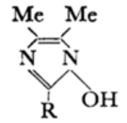
(Received October 14, 1968)

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 imidazoles[6–9] 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 discovered[15] that when aldehydes (RCHO) and butane-2,3-dione monoxime (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) led[16] to their formulation as II.


III II IV


V


VI

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

---

1) Part I, F. J. Allan and G. G. Allan, *Chem. & Ind.*, **1964**, 1837.

2) Present address, Kansai Paint Co., 27-5 Chome, Fushimi-cho, Higashi-ku, Osaka, Japan.

3) To whom inquiries should be addressed.

4) G. G. Allan, M. D. Desert, P. Mauranen and W. M. Reif, *Paperi Puu*, **50**, 529 (1968).

5) G. G. Allan, A. Lacitis, J-h. Lee, F-m. Liu and P. Mauranen, *Holzforschung*, **23**, (1969).

6) K. Hofmann, "Imidazole and Its Derivatives," Part I, Interscience Publishers, Inc., New York (1953). pp. (a) 3, (b) 13.

7) W. Schaeg, H. Finger and H. Niemann, *Biochim. Biophys. Acta*, **126**, 168 (1966).

8) S. M. Wang and N. C. Li, *J. Am. Chem. Soc.*, **88**, 4592 (1966).

9) D. M. W. Anderson, J. L. Duncan and F. T. C. Rosotti, *J. Chem. Soc.*, **1961**, 2165.

10) J. Brandrup and E. H. Immergut, "*Polymer Handbook*," Interscience Publishers, John Wiley & Sons, New York (1966), p. II-141.

11) C. Pasini and A. Vercellone, *Gazz. Chim. Ital.*, **85**, 349 (1955).

12) K. Masuda, *J. Pharm. Soc. Japan*, **76**, 325 (1956).

13) C. G. Overberger and N. Vorchheimer, *J. Am. Chem. Soc.*, **85**, 951 (1963).

14) C. G. Overberger, T. St. Pierre, C. Yaroslavsky and S. Yaroslavsky, *J. Am. Chem. Soc.*, **88**, 1184 (1966).

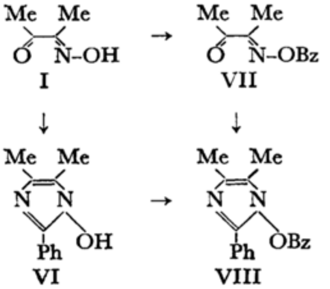
15) O. Diels, *Ber.*, **51**, 965 (1918).

16) O. Diels and C. Salomon, *ibid.*, **52**, 43 (1919).

17) W. D. Emmons, in "The Chemistry of Heterocyclic Compounds," Vol. 19, "Heterocyclic Compounds with Three- and Four-Membered Rings." Part I. ed. by A. Weissberger. Interscience Publishers, John Wiley & Sons, Inc., New York (1964), p. 624.

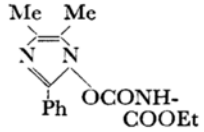
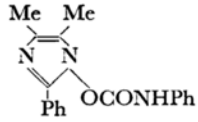
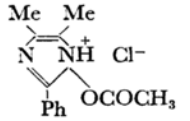
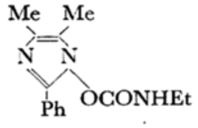
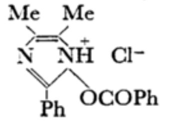
18) M. Schulz, A. Rieche and D. Becker, *Chem. Ber.*, **99**, 3233 (1966).

of IV into II and II into IV can readily be effected by crystallization from anhydrous and aqueous solvents respectively. The transition IV→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 maximum at 2240 Å (ε=8800). This is indicative 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 (τ= 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 hydrates[19] 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-2,3-dione 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 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 mistaken[24] for the parent hydroxylamine.

Table 1. Reformulated derivatives of 1-hydroxy-2-phenyl-4,5-dimethylimidazoles originally prepared by Diels anc Salomon[15]

Derivatizing reagent	Formula	Reaction product mp °C	Structure
EtOOCNCO	$C_{15}H_{17}N_3O_4$	80	
PhNCO	$C_{18}H_{17}N_3O_2$	140	
CH_3COCl	$C_{13}H_{15}N_2O_2Cl$	148	
EtNCO	$C_{14}H_{17}N_3O_2$	116	
PhCOCl	$C_{18}H_{17}N_2O_2Cl$	162	

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-hydroxybenzimidazoles[21] are known and noted for their physiological action and the closely related *N*-oxides have been described.[22-28]

---

19) J. W. Cornforth and H. T. Huang, *J. Chem. Soc.*, **1948**, 731.

20) G. de Stevens, A. B. Brown, D. Roe, H. I. Chernov and A. J. Plummer, *J. Med. Chem.*, **10**, 211 (1967).

21) O. Diels and M. Stern, *Ber.*, **40**, 1631 (1907).

22) A. T. Balaban, P. J. Halls and A. R. Katritzky, *Chem. & Ind.*, **1968**, 651.

23) A. T. Boulton, A. C. Gripper Gray and A. R. Katritzky, *J. Chem. Soc.*, B, **1967**, 911.

24) K. Volkamer, H. Bäumgartel and H. Zimmerman, *Angew. Chem. Intern. Ed.*, **6**, 947 (1967).

25) J. B. Wright, *J. Org. Chem.*, **29**, 1620 (1964).

26) G. La Parola, *Gazz. Chim. Ital.*, **75**, 216 (1945).

27) K. Bodendorf and H. Towliati, *Arch. Pharm.*, **298**, 293 (1965).

28) G. Heinning and H. Zimmerman, *Ber. Bunsenges. Phys. Chem.*, **72**, 630 (1968).

Table 2. Properties of 1-hydroxyimidazoles

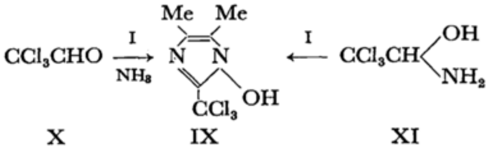
Compound*	Crystalline form**	mp °C	Yield %	Formula	% Nitrogen Calcd	% Nitrogen Found
1-Hydroxy-2,4,5-trimethylimidazole	Light tan needles[b]	62—63	77	$C_6H_{10}N_2O$	22.2	22.4
1-Hydroxy-2-ethyl-4,5-dimethylimidazole	White needles[a]	53—53.5	55	$C_7H_{12}N_2O$	20.0	20.3
1-Hydroxy-2-*iso*propyl-4,5-dimethylimidazole	White plates[a]	141—141.5	25	$C_8H_{14}N_2O$	18.1	17.7
1-Hydroxy-2-methoxymethyl-4,5-dimethylimidazole	White needles[c]	234—236	10	$C_7H_{12}N_2O_2$	17.9	18.1
1-Hydroxy-2-(1-methyl-*n*-butyl)-4,5-dimethylimidazole	White needles[a]	125—127	25	$C_{10}H_{18}N_2O$	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)	18	$C_6H_7N_2OCl_3$	12.2	12.1
1-Hydroxy-2-vinyl-4,5-diphenylimidazole	Tan needles[c]	180—184	15	$C_{17}H_{14}N_2O$	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-*n*-pentyl)-4,5-diphenylimidazole	White needles[c]	234—235	85	$C_{22}H_{26}N_2O$	8.4	8.9
1-Hydroxy-2-methyl-4,5-diphenylimidazole	Pinkish white rhomboids[c]	247—248	20	$C_{16}H_{14}N_2O$	11.2	10.7
1-Hydroxy-2-phenylphenanthrimidazole***	Colorless needles[c,e]	280—282	34	$C_{21}H_{14}N_2O$	9.0	8.9

* 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, [e] dimethylformamide.

*** The hydrate[24] has mp 235—238°C.

Since the formation of these 1-hydroxyimidazoles probably requires the genesis of an aldehyde-ammonia 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.



X IX XI

The versatility of this synthetic route to 1-hydroxyimidazoles 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. 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 m*l*/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-4,5-dimethylimidazole (0.859 g, 3.4 mmol) in dioxan (200 m*l*) 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 m*l*) 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 $C_{18}H_{16}N_2O_2$: 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 m*l*) was treated with butane-2,3-dione monoxime benzoate[20] (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 $C_{18}H_{16}N_2O_2$: N, 9.6%.

1-Hydroxy-2-trichloromethyl-4,5-dimethylimidazole (IX). a) A solution of trichloroacetaldehyde (2.94 g,

---

[29] R. Schiff, *Ber.*, **10**, 167 (1877).

0.02 mol) and butane-2,3-dione monoxime (2.02 g, 0.02 mol) in dioxan (6 m*l*) was treated at room temperature with aqueous ammonia (*d*, 0.88, 1.6 m*l*) 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 m*l*) was allowed to stand overnight, the material which had separated was recrystallized from acetone-hexane to yield white needles (0.6 g, 14% yield), mp 178—182°C (dec.). This product showed no mp depression when mixed with IX prepared in a). IR spectra of the two products were superimposable.

Found: N, 12.15%. Calcd for $C_6H_7N_2OCl_3$: N, 12.20%.

Financial aid (to T.F.) was provided by the Undergraduate Research Participation Program of the National Science Foundation. One of us (K.A.) thanks the Kansai Paint Co. for support during a study leave.