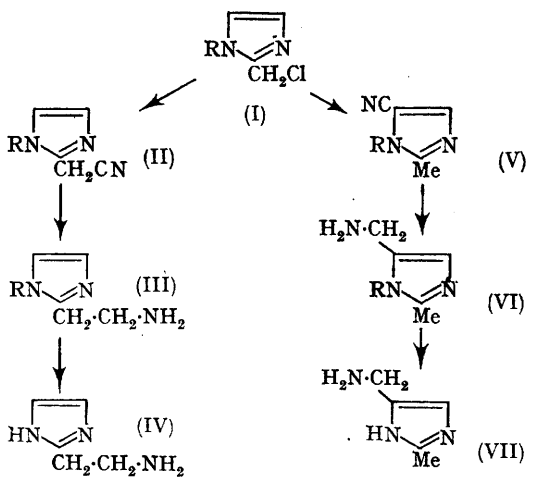
Isohistamine [2-(2-Aminoethyl)imidazole]

By G. J. DURANT, M. E. FOOTTIT, C. R. GANELLIN, J. M. LOYNES, E. S. PEPPER, and A. M. ROE*
(*Smith Kline and French Research Institute, Welwyn Garden City, Hertfordshire*)

SUBSTITUTION with rearrangement (S_N') of chlorine by cyanide is rarely observed with chloromethyl heterocyclic compounds.[1] Prompted by the disclosure[2] of unpublished work by Gutsche and Gitel, we report rearrangements of this type in the imidazole series, detection of which has enabled us to explain some of the anomalous properties of the compound reported[3] to be 2-(2-aminoethyl)-imidazole (IV). Since (IV) is a positional isomer of histamine, [4(5)-(2-aminoethyl)imidazole], we refer to it as isohistamine.

In our hands the reported synthesis of (IV) (Scheme 1) from the chloride (Ia) by cyanide replacement followed by reduction and debenzylation [*i.e.* the route reported to give structures (IIa) and (IIIa)], proceeded ostensibly as described;[3] however, the n.m.r. spectrum of the product (see Table) clearly shows that it is not (IV) but (VII). The n.m.r. spectra of the two intermediate products are also incompatible with structures (IIa) and (IIIa) and support their formulation as (Va) and (VIa). That we have obtained the same compounds as Jones[3] can be seen from the close agreement of their melting



a, R=$PhCH_2$; b, R=Me

SCHEME 1

points (see Table). Thus it appears that (Ia) has undergone nuclear substitution by cyanide ion

TABLE

Melting points and nuclear magnetic resonance spectra

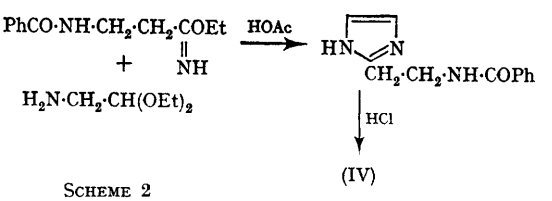
Compound[a]	M.p.	Literature structure and m.p.	Chemical shift (τ)[b]	Multiplicity[c]	Relative intensity	Assignment
			2·22 2·31	q[g]	2	4-H, 5-H
(Ia) HCl[d,e]	187°	(Ia)[f] 181—182°	4·34	s	2	CH_2Ph
			4·74	s	2	CH_2Cl
(Va) base	123—124	(IIa)[f] 114—115	1·63	s	1	4-H
HCl[d,e]	177—178·5	—	4·38	s	2	CH_2Ph
picr.	167—169	166—167	7·15	s	3	CH_3C
(VIa) base	61·5—63·5	(IIIa)[f] 59—60	2·22	t[h]	1	4-H
2HCl[d,e]	226—228	224—225	4·39	s	2	CH_2Ph
dipicr.	189—191 (decomp.)	185—186	5·62	d[h]	2	CH_2N
			7·26	s	3	CH_3C
(VII) 2HCl[d,e]	229·5—231 (decomp.)	(IV)[f] 229—230	2·42	bs	1	4-H
dipicr.	213—214 (decomp.)	213—214 (decomp.)	5·60	d[i]	2	CH_2N
			7·31	s	3	CH_3C
(IV) 2HCl[d,e]	262—263 (decomp.)	— —	2·58	s	2	4-H, 5-H
dipicr.	217—218 (decomp.)	—	6·52	s	4	CH_2CH_2
			2·43 2·46	q[k]	2	4-H, 5-H
(Ib) HCl[d,e]	175—177	(Ib)[j] 168	4·92	s	2	CH_2Cl
			6·01	s	3	CH_3N
			2·24 2·31	q[g]	2	4-H, 5-H
(IIb) HCl	235—237 (decomp.)	(IIb)[j] —	5·31	s[m]	2	CH_2CN
picr.[d,l]	179—180 (decomp.)	165—166	6·08	s	3	CH_3N
(Vb) base	54—57	— —	1·53	s	1	4-H
picr.[d,l]	211—212		6·17	s	3	CH_3N
		—	7·35	s	3	CH_3C

[a] All compounds had satisfactory micro-analyses; n.m.r. spectra were determined on a Varian A60A spectrometer using approximately 10% w/v solutions. [b] Signals from phenyl-, picryl-, and N–H protons are omitted from this Table. [c] s = singlet, d = doublet, t = triplet, q = quartet, and bs = broad singlet. [d] Compound used for n.m.r. determination. [e] Determination in D_2O using sodium 2,2-dimethyl-2-silapentane-5-sulphonate as internal reference. [f] Reference 3. [g] J(4-H,5-H) = 2·0 c./sec. [h] $J(CH_2,4\text{-H})$ = 0·9 c./sec. [i] $J(CH_2,4\text{-H})$ = 0·8 c./sec. [j] Reference 8. [k] Incompletely resolved. [l] Determination in $(CD_3)_2SO$ using tetramethylsilane as internal reference. [m] When the spectrum of (IIb), HCl was determined in D_2O, the CH_2 signals were not observed, indicating rapid proton-deuteron exchange with this solvent.

with displacement of chloride ion, followed by rearrangement of a proton. Presumably this occurs *via* the intermediate (VIII) which leads to the 1,2,5-trisubstituted imidazole (Va) rather than the alternative 1,2,4-trisubstituted isomer.

Reformulation of (IV) as (VII) provides an explanation for the much discussed[4,5] absence of histamine-like activity of this compound, since 4(5)-aminomethylimidazole and related compounds with a one carbon side-chain are known to be inactive.[5a] This reformulation also explains the observations which led Holmes and Jones[6] to adumbrate that isohistamine formed a 5-membered ring chelate with metal ions.

We now report the synthesis of authentic isohistamine (IV) by the route shown (Scheme 2).[7]

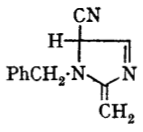


SCHEME 2

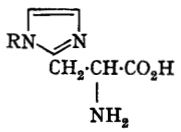
The product (which can be obtained in 50% overall yield) has an n.m.r. spectrum which confirms its

structure (see Table). The biological activity of isohistamine resembles that of histamine but it is much less potent.†

The generality of this rearrangement is being examined. We have shown that nucleophilic displacement of chloride in (Ia) by sodium diethyl acetamidomalonate[3] occurs without rearrangement; and, after hydrolysis and decarboxylation, 1-benzylimidazol-2-ylalanine (IX; R = $PhCH_2$) is obtained which can be debenzylated[3] to isohistidine (IX; R = H).‡



(VIII)



(IX)

The action of cyanide on (Ib) has been reported[8] to give (IIb), isolated as its picrate. We find that the product of this reaction is in fact a mixture, from which we have separated and fully characterized the nitriles, (IIb) and (Vb) (see Table).

(*Received, December 4th*, 1967, *Com.* 1286.)

† Measured on the isolated guinea pig ileum and on the secretion of acid by the perfused rat stomach. We thank our colleagues Dr. J. W. Black, Mr. K. E. V. Spencer, and Mr. M. E. Parsons for these results.

‡ Melting points of these products indicate that we have prepared the same compounds as Jones (ref. 3) and their n.m.r. spectra are in agreement with structures (IX; R = $PhCH_2$ and H).

[1] One such example, the conversion of 2-chloromethylfuran into a mixture of 2-cyanomethylfuran and 2-cyano-5-methylfuran has been studied in some detail [K. Y. Novitskii, K. Gresl, and Y. K. Yurev, *Khim. geterotsikl., Soedinenii*, 1966, 829; Y. Ohshiro, H. Tanisake, and S. Komori, *J. Soc. Org. Synthetic Chem.* (*Japan*), 1966, **24**, 950]. Related rearrangements have been described with 3-chloromethylfuran (E. Sherman and E. D. Amstutz, *J. Amer. Chem. Soc.*, 1950, **72**, 2195), 3-chloromethylbenzo[*b*]thiophen (E. Campaigne and W. M. LeSuer, *J. Amer. Chem. Soc.*, 1948, **70**, 1555), and 3-trimethylammonium-methylindole (H. R. Snyder and E. L. Eliel, *J. Amer. Chem. Soc.*, 1948, **70**, 1857).

[2] C. D. Gutsche and H. Voges, *J. Org. Chem.*, 1967, **32**, 2685.

[3] R. G. Jones, *J. Amer. Chem. Soc.*, 1949, **71**, 383.

[4] H. M. Lee and R. G. Jones, *J. Pharmacol. Exp. Therap.*, 1949, **95**, 71; P. C. Jocelyn, *Arch. int. Pharmacodyn.*, 1958, **113**, 251.

[5] "Handbook of Experimental Pharmacology", Vol. XVIII/1, "Histamine and Anti-Histaminics, Part 1", ed. M. Rocha e Silva, Springer-Verlag, New York, 1966: (a) R. G. Jones, p. 34; (b) M. Rocha e Silva, p. 234.

[6] F. Holmes and F. Jones (*J. Chem. Soc.*, 1962, 2818) stated that values for the formation constants of complexes of copper and nickel with compound (VII), were more like those for compounds that formed 5-membered ring chelates, whereas (IV) should have given similar constants to those of histamine.

[7] This method is an adaptation of that used for the synthesis of several analogous 2-(2-aminoethyl)imidazoles (L. P. Ellinger and A. A. Goldberg, *J. Chem. Soc.*, 1949, 263; B.P., 625,442/1949).

[8] P. C. Jocelyn, *J. Chem. Soc.*, 1957, 3305.