Synthesis of 4(5)-Substituted 2-Amino-5(4)-Hydroxyimino-5(4)*H*-imidazoles and Their Transformation into the Corresponding 3-Substituted 5-Amino-1,2,4-oxadiazoles

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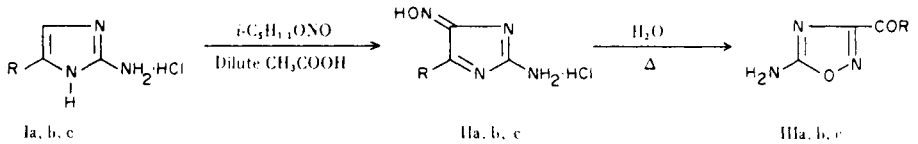
Treatment of 4(5)-phenyl(or alkyl)-2-aminoimidazoles with isoamyl nitrite in acetic acid afforded the corresponding 4(5)-substituted 2-amino-5(4)-hydroxyimino-5(4)*H*-imidazoles which by heating in water were transformed into 3-benzoyl(or acyl)-5-amino-1,2,4-oxadiazoles.

Treatment of 2-aminoimidazoles with nitrous acid was formerly thought to produce nitroso derivatives (2), rather than diazo compounds, and this was taken as evidence of the non-aromaticity of 2-aminoimidazoles (3,4). Subsequently, it was shown (5,6,7,8) that under strongly acidic conditions these compounds can be diazotized, as demonstrated by their conversion into nitroimidazoles upon treatment with nitrous acid and copper catalyst. In one instance (9), the 4,5-diphenyl-2-diazoimidazole was isolated as such.

Scheme I



Ia, b, c — IIa, b, c — IIIa, b, c

a, R = C_6H_5
b, R = CH_3
c, R = n-C_3H_7

Scheme II

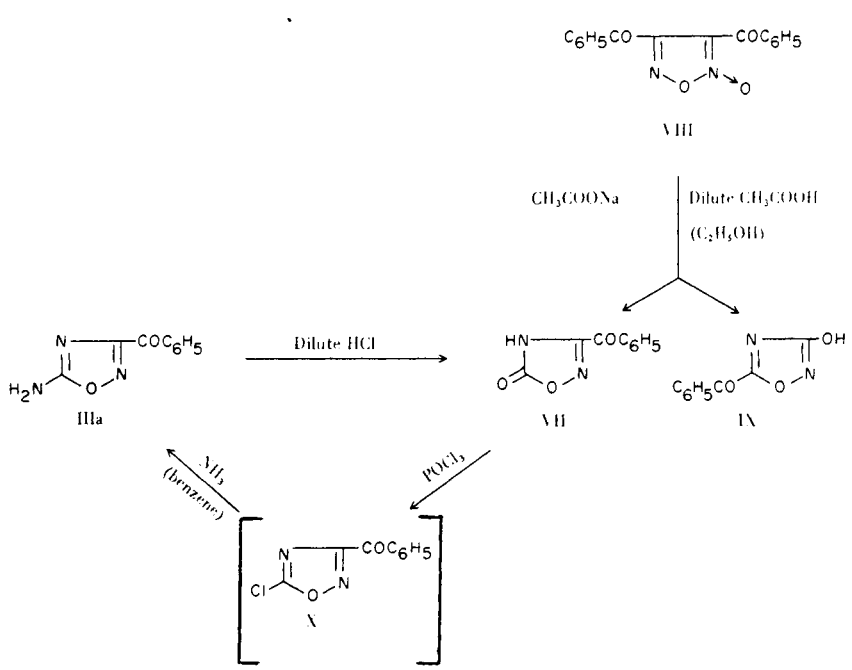
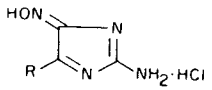


TABLE I

4(5)-Substituted 2-amino-5(4)-hydroxyimino-5(4)*H*-imidazoles Hydrochlorides

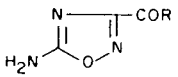


Compound	R	Yield (a) %	M.p., °C	Recrystallization Solvent	Molecular Formula (b)	Elemental Analysis Calcd. C	H	Cl	N	Found C	H	Cl	N
IIa	C_6H_5	88.6	158-160 (c) 165	Methanol-ethyl ether	$C_9H_8N_4O$·HCl ·CH_3OH	46.79	5.10	13.81	21.81	46.74	5.23	13.53	21.47
IIb	CH_3	82.2	175-180 278 dec.	Methanol-isopropyl ether	$C_4H_6N_4O$·HCl ·CH_3OH (d)	30.87	5.69	18.21	28.79	30.91	5.98	18.33	28.35
IIc	n-C_3H_7	79.3	125-130 (c) 135	Methanol-isopropyl ether	$C_6H_{10}N_4O$·HCl ·CH_3OH	37.75	6.79	15.92	25.16	37.55	6.40	16.24	24.84

(a) Crude material. (b) All products retain one molecule of methanol of crystallization (detected by gpcf). (c) Melting transformation. (d) Determination of 0: Calcd.: 16.44. Found: 16.00.

TABLE II

3-Substituted 5-amino-1,2,4-oxadiazoles



Compound	R	Yield % (a)	M.p., °C	Recrystallization Solvent	Molecular Formula (b)	Elemental Analysis Calcd. C	H	N	Found C	H	N
IIIa	C_6H_5	97.8 (a)	193	Dilute Ethanol	$C_9H_7N_3O_2$	57.14	3.73	22.21	56.78	4.09	22.03
IIIb	CH_3	94.9 (a)	210-211	Water	$C_4H_5N_3O_2$	37.80	3.97	33.06	37.88	4.20	33.40
IIIc	n-C_3H_7	73.2	174-175	Dilute Ethanol	$C_6H_9N_3O_2$	46.45	5.85	27.08	46.24	6.17	27.16

(a) Crude material. (b) Molecular weight confirmed by the M^+ peak in the mass spectrum.

TABLE III

Derivatives of 3-Substituted 5-amino-1,2,4-oxadiazoles

Compound	R	X	M.p., °C	Recrystallization Solvent	Molecular Formula	Elemental Analysis					
						C	Calcd. H	N	C	Found H	N
IVa	C_6H_5	N-NH-$C_6H_3(NO_2)_2$-*o,p*	212-213	Ethanol (a)	$C_{15}H_{11}N_7O_5$	48.79	3.00	26.55	48.78	3.05	26.65
Va	C_6H_5	NOH	209-210	Ethanol	$C_9H_8N_4O_2$	52.94	3.95	27.44	52.76	3.95	27.45
IVb	CH_3	N-NH-$C_6H_3(NO_2)_2$-*o,p*	242-244	Ethanol	$C_{10}H_9N_7O_5$	39.10	2.96	31.91	39.13	3.27	32.10
Vb	CH_3	NOH	210	Water	$C_4H_6N_4O_2$	33.81	4.26	39.42	33.92	4.34	39.48
VIb	CH_3	N-NH-CS-NH_2	200	Water	$C_5H_8N_6OS$	29.99	4.03	41.97	30.37	4.31	41.60
IVc	*n*-C_3H_7	N-NH-$C_6H_3(NO_2)_2$-*o,p*	204-206	Ethyl Acetate	$C_{12}H_{13}N_7O_5$	42.98	3.91	29.25	42.65	4.36	29.55
Vc	*n*-C_3H_7	NOH	182-183	Water	$C_6H_{10}N_4O_2$	42.35	5.92	32.92	41.95	6.25	32.95

(a) Containing 2% of dimethylformamide.

During attempts for improving the diazotization reaction 4(5)-phenyl(or alkyl)-2-aminoimidazoles hydrochlorides (I) were treated with isoamyl nitrite in acetic acid obtaining colorless products to which the structure of the corresponding 4(5)-substituted 2-amino-5(4)-hydroxyimino-5(4)*H*-imidazoles hydrochlorides (IIa, b, c) was assigned.

Compounds IIa, b, c as obtained from the reaction mixture strongly retain one molecule of water of crystallization (confirmed both by gpcf and thermal analysis); when they are recrystallized from low boiling alkanols, the water is substituted by one molecule of the alcohol (confirmed as above). Compound IIb (R = CH_3) gives a weak yellow color with sodium hydroxide, while compound IIa (R = C_6H_5) gives an intense red color; both give a positive Liebermann's test (10). A silver salt of IIb was prepared, from which the compound can be regenerated.

The absence in the pmr spectra (DMSO-d_6) of the band at δ 6.60-6.70 corresponding to the absorbance of the proton in position 4 in the 2-aminoimidazoles indicates substitution at that position. Concerning the tautomeric form, the pmr spectra are not diagnostic since mobile hydrogens appear as a unique broad band. Ir spectra (Nujol) show bands at 3400-3250 and 3150-3100 cm^{-1} (ν OH), 2800-2000 cm^{-1} (ν NH_3^+), 965-960 cm^{-1} (ν N-O). The strong band at 965 cm^{-1} which is characteristic for the ν N-O absorption of the oximes, is still present in a small sample of IIb dehydrated by carefully heating at 150° *in vacuo*.

The reaction failed when position 4 or the nitrogen in position 1 are carrying substituents, confirming that the nitrosation takes place in position 4. All the above evidence appears to be consistent with the hydroxyimino tautomeric form, which is probably the more stable one.

The introduction of the -NO or =NOH function at position 4 is in accordance with the general behavior of imidazoles towards the nitrosation reaction described by S. Cusmano *et al.* (11,12).

We have examined the behavior of compounds IIa, b, c upon boiling in water, and we have obtained ammonium chloride and compounds IIIa, b, c which do not possess the imidazole structure, nor give color with sodium hydroxide and are negative to the test for the nitroso-isonitroso group. These compounds contain a carbonyl function which reacts with 2,4-dinitrophenylhydrazine (IVa, b, c), with hydroxylamine (Va, b, c) and with thiosemicarbazide (VIb) (Table III). These results indicate a transformation of II into 3-substituted 5-amino-1,2,4-oxadiazoles (III) according to the well-known behavior of 2,4(5)-disubstituted-5(4)-nitrosoimidazoles which by hydrolytic opening of the imidazole ring and subsequent cyclization afford 3,5-disubstituted-1,2,4-oxadiazoles (13).

TABLE IV

PMR (DMSO-d_6) Data of 3-Substituted-5-amino-1,2,4-oxadiazoles and Derivatives

Compound	δ (ppm)	Multiplicity	Assignment
IIIa	6.65	s	NH_2 (2H)
	7.4-7.9 and 8.1-8.4	2m	C_6H_5 (5H)
IIIb	2.57	s	CH_3 (3H)
	8.22	s	NH_2 (2H)
IIIc	0.93	t	$CH_3C(H_2)$ (3H)
	1.35-2.05	m	$C(H_3)$-CH_2 (2H)
	2.93	t	$C(H_2)$-CH_2-CO (2H)
	8.18	s	NH_2 (2H)
IVa	6.34	s	NH_2 (2H)
	7.35-8.05	m	C_6H_5 (5H)
	8.43	d	H aromatic in 6 (1H)
	8.71	2d	H aromatic in 5 (1H)
	8.90	s	NH (1H)
	9.03	d	H aromatic in 3 (1H)
IVb	2.34	s	CH_3 (3H)
	6.55	s	NH_2 (2H)
	8.33	d	H aromatic in 6 (1H)
	8.64	2d	H aromatic in 5 (1H)
	8.95	d	H aromatic in 3 (1H)
	9.25	s	NH (1H)
IVc	0.98	t	CH_3 (3H)
	1.2-2.3	m	$C(H)_3$-CH_2 (2H)
	2.68	t	$C(H_2)$-CH_2-C=
	7.98	d	H aromatic in 6 (1H)
	8.35	s	NH_2 (2H)
	8.40	2d	H aromatic in 5 (1H)
	8.85	d	H aromatic in 3 (1H)
	13.40	s	NH (1H)
Va	6.55	s	NH_2 (2H)
	7.45-8.00	m	C_6H_5 (5H)
	9.05	s	NOH (1H)
Vb	2.08	s	CH_3 (3H)
	7.80	s	NH_2 (2H)
	11.86	s	NOH (1H)
Vc	0.90	t	CH_3-$C(H_2)$ (3H)
	1.25-1.95	m	$C(H_3)$-CH_2 (2H)
	2.63	t	$C(H_2)$-CH_2-C=
	7.88	s	NH_2 (2H)
	11.80	s	NOH (1H)

The structure of 3-aroyl(or acyl)-5-amino-1,2,4-oxadiazoles for compounds IIIa, b, c is confirmed by ir spectra (Nujol) which exhibit bands at 3400-3300 and 3200-3100 cm^{-1} (ν NH_2), 1680-1650 cm^{-1} (ν C=O) and bands at 1570, 1350-1225, 1180-1140 and 920-883 cm^{-1} which are characteristic of 1,2,4-oxadiazoles (14,15).

Further confirmation of structure III was chemically obtained on compound IIIa by transforming it by hydrolysis with hydrochloric acid into 3-benzoyl-1,2,4-oxadiazolin-5-one (VII), which was identical with the compound prepared [together with the isomeric 3-hydroxy-5-benzoyl-1,2,4-oxadiazole (IX)] by mild hydrolysis of the dibenzoylfuroxan as reported by Ponzio (16) (Scheme II). Reaction of compound VII with phosphorus oxychloride gave the chlorinated intermediate X which was not isolated in a pure state. The latter treated with ammonia afforded compound IIIa. This procedure parallels the behavior of 3-phenyl-1,2,4-oxadiazolin-5-one (17).

The structure of 3-benzoyl-5-amino-1,2,4-oxadiazole was assigned by J. Böeseken (18) to the product, m.p. 135° obtained by treating dibenzoylfuroxan with diluted ammonia solution, but further investigation (19,20) proved that it was 3-amino-4-benzoyl-1,2,5-oxadiazole (21). Thus, to our knowledge, no example of 3-acyl(or aroyl)-5-amino-1,2,4-oxadiazoles has been reported in literature.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. Ir spectra were obtained on a Perkin-Elmer Model 157 spectrophotometer, as Nujol mulls. Uv spectra were recorded with a Unicam SP 800 spectrophotometer. Pmr spectra were obtained on a Varian A-60 (60 MHz) spectrometer in DMSO-d_6. Chemical shifts are reported as δ relative to TMS (δ = 0.00 ppm), using the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. Thin-layer chromatographies (tlc) were performed on Silica gel HF/UV_{254} to a distance of 10.0 cm. Spots were detected by visual examination under uv light and after spraying with a 0.01% aqueous solution of fluorescein and then with concentrated sulfuric acid.

2-Amino-4(5)-hydroxyimino-5(4)-phenyl-4(5)*H*-imidazole Hydrochloride (IIa).

To a solution of 8.4 g. (0.043 mole) of 4(5)-phenyl-2-aminoimidazole hydrochloride (Ia) (22) in 175 ml. of water and 250 ml. of glacial acetic acid, 5.9 ml. (0.044 mole) of isoamyl nitrite was added dropwise during 15 minutes, the temperature being kept at 0-5°. The solution was stirred for 1 hour at 0°, then for 3 hours at room temperature. The mixture was concentrated *in vacuo* at room temperature to give a solid which was filtered, washed with glacial acetic acid and then with ethyl ether (8.5 g.). Recrystallization from methanol-ethyl ether gave colorless crystals, m.p. 158-160°. The product retains one molecule of methanol of crystallization; tlc (developed with a 95:5 mixture of methanol-acetic acid) R_f = 0.68; ir: 3200 and 3100 (ν OH), 2800-2000 (ν NH_3^+), 1700 (ν C=N), 1550 (δ NH_3^+), 960 (ν N-O), 705 cm^{-1} (γ aromatic CH); pmr: δ 3.20 (s, 3H, CH_3O), δ 7.49 (s, 5H, C_6H_5), δ 8.1-11.7 (m, 5H, mobile H).

2-Amino-4(5)-hydroxyimino-5(4)-methyl-4(5)*H*-imidazole Hydrochloride (IIb).

It was obtained by the same procedure described above starting from 4(5)-methyl-2-aminoimidazole hydrochloride (Ib) (22). The product crystallizes with one molecule of methanol; tlc (developed with a 95:5 mixture of methanol-acetic acid) R_f = 0.65; ir: 3400 and 3150 (ν OH), 2800-2000 (ν NH_3^+), 1700 (ν C=N), 1545 (δ NH_3^+), 965 (ν N-O); pmr: δ 1.62 (s, 3H, CH_3-CO), δ 3.22 (s, 3H, CH_3O), δ 8.0-12.8 (m, 5H, mobile H).

2-Amino-4(5)-hydroxyimino-5(4)-*n*-propyl-4(5)*H*-imidazole Hydrochloride (IIc).

This compound was prepared by the same procedure starting from 4(5)-*n*-propyl-2-aminoimidazole hydrochloride (Ic) (23). The product crystallizes with one molecule of methanol; tlc (developed with a 95:5 mixture of methanol-acetic acid) R_f = 0.63; ir: 3250 and 3150 (ν OH), 2800-2000 (ν NH_3^+), 1700 (ν C=N), 1550 (δ NH_3^+), 960 cm^{-1} (ν N-O); pmr: δ 1.0 [t, 3H, CH_3-$C(H_2)$], δ 1.2-2.7 (m, 4H, CH_2CH_2), δ 3.22 (s, 3H, CH_3O), δ 8.2-11.4 (m, 5H, mobile H).

3-Benzoyl-5-amino-1,2,4-oxadiazole (IIIa).

(a).

A suspension of 5.4 g. (0.021 mole) of crystallized IIa in 60 ml. of water was heated to boiling. After a few minutes, the solid dissolved and then a precipitate was formed. The mixture was refluxed for one hour, cooled and the product was collected, washed with water and dried to give 3.8 g. of IIIa, m.p. 193°; tlc (developed with a 1:9 mixture of methanol-chloroform) R_f = 0.32; uv λ max (methanol) (log ϵ), 258 mμ (4.09); ir: 3400 and 3160 (ν NH_2), 1650 (ν C=O), 1600 and 1500 (ν aromatic C=C), 1570, 1225, 1180, and 920 (skeletal vibration of heterocyclic ring), 730 and 680 cm^{-1} (γ aromatic CH).

(b).

A mixture of 1.4 g. (0.0073 mole) of VII, 6.7 ml. of phosphorus oxychloride and 0.25 ml. of pyridine was heated at 130° (bath temperature) for seven hours. After cooling, the solution was poured into ice-water and extracted with chloroform. The extract was washed with water, dried on sodium sulphate and concentrated under reduced pressure. An oily residue (1.4 g.) was obtained which was dissolved in anhydrous benzene, saturated with ammonia and allowed to stand at room temperature for two days. The precipitate was filtered off and the solution was evaporated to dryness, obtaining a crude product which was triturated with water, filtered and recrystallized from diluted ethanol. Yield 0.65 g. (46.4%) of a compound which showed a good analysis for $C_9H_7N_3O_2$ and was identical through mixed m.p., tlc, ir, and pmr spectra with IIIa obtained as described above.

3-Acetyl-5-amino-1,2,4-oxadiazole (IIIb).

This compound was prepared as above from IIb; tlc (developed with a 1:9 mixture of methanol-chloroform) R_f = 0.24; ir: 3300 and 3100 (ν NH_2), 1680 (ν C=O), 1570, 1350, 1175, and 883 cm^{-1} (skeletal vibration of heterocyclic ring).

3-Butyryl-5-amino-1,2,4-oxadiazole (IIIc).

This compound was prepared similarly from IIc; tlc (developed with a 1:9 mixture of methanol-chloroform) R_f = 0.36; ir: 3400 and 3200 (ν NH_2), 1670 (ν C=O), 1570, 1340, 1140, and 890 cm^{-1} (skeletal vibration of heterocyclic ring).

Derivatives of the 3-substituted 5-amino-1,2,4-oxadiazoles (IV, V, VI) (Table III).

These derivatives were prepared according to the normal procedures and checked by tlc. Ir spectra are as expected. Pmr spectra are given in Table IV.

3-Benzoyl-1,2,4-oxadiazolin-5-one (VII).

(a) By Hydrolysis of Compound IIIa.

Compound IIIa (1 g.) was refluxed with 40 ml. of 27% hydrochloric acid for 2 hours. By cooling, a crystalline compound separates which was filtered and washed with ice-water, 0.15 g., m.p. 188-189°; tlc (developed with a 95:5 mixture of methanol-acetic acid) R_f = 0.67; uv λ max (ethanol) (log ϵ), 264 (4.02), 287 mμ (shoulder); ir: 3150 (ν NH), 1790 (ν lactone C=O), 1670 (ν ketone C=O), 1585 (ν aromatic C=C), 1570, 1300, 1240 and 883 (skeletal vibration of heterocyclic ring), 725 and 680 cm^{-1} (γ aromatic CH); pmr: δ 7.4-7.9 and 8.0-8.4 (two m, 6H, C_6H_5 and OH).

Anal. Calcd. for $C_9H_6N_2O_3$: C, 56.85; H, 3.18; N, 14.73. Found: C, 56.56; H, 3.57; N, 14.32 (24).

Concentration of the filtrate and extraction with ether gave 0.4 g. of an oily product which was found to be crude phenylglyoxylic acid (ir spectrum). Complete evaporation of the water gave ammonium chloride.

(b) By Hydrolysis of Dibenzoylfuroxan (VIII).

By treating VIII under the mild hydrolysis conditions described by Ponzio (16) a product, m.p. 190° was obtained (lit. (16) 192-193°). Mixed m.p. with compound VII prepared as described under (a) was without depression, and the uv, ir, and pmr spectra were identical. In the same experiment, 3-hydroxy-5-benzoyl-1,2,4-oxadiazole (IX) was isolated, which melts at 125° (lit. (16) 123-124°); uv λ max (ethanol) (log ε), 261 mμ (4.10); ir: 3310 (ν OH), 1650 (ν ketone C=O), 1595 and 1500 (ν C=C), 1580, 1175, and 925 (skeletal vibration of heterocyleic ring), 750 and 680 cm^{-1} (γ aromatic CH).

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