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SYNTHESIS AND PROPERTIES OF 4-HALOIMIDAZO[4,5-c]PYRIDIN-2-ONES

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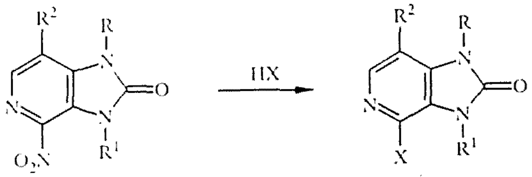
The nitro group in 4-nitroimidazo[4,5-c]pyridin-2-ones is rather labile and may be replaced upon heating with hydrohalic acids to give the corresponding 4-halides. A methyl group at $N_{(3)}$ *leads to a sharp increase in the lability of the nitro group, but the isomeric 5-nitro derivatives do not react with hydrobromic or hydrochloric acids. Some reactions and transformations of 4-chloroimidazo[4,5-c]pyridin-2-one are examined.*

In a study of the chemical properties of 4-nitro-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (Ia) and its derivatives Ib-If [1], we noted that the nitro groups in these compounds are replaced by halogen upon reaction with hydrochloric and hydrobromic acids [2, 3]. These transformations may be compared with the analogous processes for 2- and 4-nitropyridines [4, 5].

Indeed, heating Ia and Ib with concentrated hydrochloric acid at 150-160°C is accompanied by the release of nitrogen oxides and leads to compounds identical to 4-chloro-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (IIa) and its 1-methyl derivative (IIb) [6].

The reaction of nitro derivatives Ia and Ib with hydrobromic acid under the same conditions gave 4-bromoimidazo-[4,5-c]pyridin-2-ones IIg and IIh. However, a methyl group at $N_{(3)}$ in compounds such as Ic, Id, and If not only does not hinder replacement of the nitro group by chlorine or bromine but rather significantly facilitates this replacement. These compounds begin to react noticeably with the indicated acids already upon raising the temperature above 50°C. Brief heating of the reaction mixture at reflux gives conversion to halides IIc, IId, IIf, IIi, IIj, and II*l* in high yield. The course of the reaction may initially be monitored visually relative to the release of nitrogen dioxide and, at the end of the reaction, by holding starch—iodine paper above the mixture. Nitrogen oxides are not released if the reaction is carried out in the presence of urea. Heating nitro compound Id with 42% hydrofluoric acid and urea gave 4-fluoro-1,3-dimethylimidazo[4,5-c]pyridin-2-one (IIm) in 67% yield. On the other hand, the reaction of these nitro compounds with hydriodic acid leads only to formation of the corresponding amines, as reported in our previous work [1].



I a-f   II a-i

Ia, IIa, g $R = R^1 = R^2 = H$; Ib, IIb, h $R^1 = R^2 = H$, $R = CH_3$; Ic, IIc, i $R = R^2 = H$, $R^1 = CH_3$; Id II d,j,m $R^1 = R = CH_3$, $R^2 = H$; Ie, IIe, k $R = R^1 = H$, $R^2 = Br$; If, IIf, *l* $R = R^1 = CH_3$, $R^2 = Br$; IIa—f $X = Cl$; II g-*l* $X = Br$; IIm $X = F$

The replacement of the nitro group in IIe and IIf by halogen gave previously unreported 4,7-dihalides IIe, IIf, IIk, and II*l*. Starting nitro compound Ie was obtained under conditions analogous to those described in our previous work [1] by the nitration of 7-bromoimidazo[4,5-c]pyridin-2-one (III). Methylation of Ie in alkaline medium gave If. In turn, base III is obtained by fusing 5-bromo-3,4-diaminopyridine [7] with urea.

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TABLE 1. 4-Haloimidazo[4,5-c]pyridin-2-ones (IIb)-(IIm)

Compound	Chemical formula	T_{mp}, °C	Yield, %
IIb	—	267...268[*2]	95
IIc	$C_7H_6ClN_3O$	316...317	80
IId	$C_8H_8ClN_3O$	199...200	96
IIe	$C_6H_3BrClN_3O$	400	87
IIf	$C_8H_7BrClN_3O$	152...153	84
IIg	$C_6H_4BrN_3O$	334...336	80
IIh	$C_7H_6BrN_3O$	284...285	70
IIi	$C_7H_6BrN_3O$	313	66
IIj	$C_8H_8BrN_3O$	194	87
IIk	$C_6H_3Br_2N_3O$	400	60
II*l*	$C_8H_7Br_2N_3O$	164	94
IIm	$C_8H_8FN_3O$	159...160	67

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[*] Products IIb, IId, IIf, IIh, IIi, and IIj were recrystallized from ethanol, IIe and IIk from DMF, IIc from nitromethane, II*l* from hexane, IIi from dioxane, and IIg was reprecipitated from solution in a solution obtained by mixing one part hydrochloric acid and 10 parts water.

[*2] Mp. 267-268°C [6].

TABLE 2. PMR Spectra of IIb-IId and IIh-IIm in CF_3CO_2H

Compound	Chemical shift, δ, ppm				Coupling constant, $J_{6,7}$, Hz
	$1\text{-}CH_3$	$3\text{-}CH_3$	6-H d	7-H d	
IIb	3.70	—	8.50	7.69	6.9
IIc	—	3.88	8.36	7.82	6.6
IId	3.70	3.90	8.40	7.61	6.7
IIh	3.69	—	8.46	7.65	6.7
IIi	—	3.93	8.44	7.87	7.0
IIj	3.64	3.91	8.40	7.61	6.8
IIk	—	—	8.45	—	—
II*l*	3.92	4.01	8.52	—	—
IIm	3.70	3.79[*]	8.26[*2]	7.56	6.7

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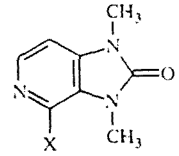
[*] J_{FH} = 1.2 Hz, doublet.

[**] J_{FH} = 1.9 Hz, multiplet.

The PMR spectra of halides IIb-IId and IIh-IIj are similar to each other and analogous to the spectra of the starting nitro compounds [1] (Table 2). Splitting of the signals of one of the N-methyl groups (J_{FH} = 1.2 Hz) and H-6 (J_{FH} = 1.9 Hz) is observed in the PMR spectrum of base IIi due to a spin—spin interaction with the fluorine atom.

It is interesting to note that 5-nitro-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one and its N-substituted derivatives [8], which are isomers of Ia-Id, do not react with either hydrobromic or hydrochloric acid at up to 190°C. The enhanced lability of the nitro group in Ic, Id, and If is in accord with a steric interaction of the nitro group and methyl group at $N_{(3)}$, which leads to a loss of molecular planarity due to twisting of the plane of the nitro group relative to the plane of the bicyclic ring system. This, in turn, should lead to a decrease in the order of the C—NO_2 bond and enhancement of its polarization. Indeed, comparison of the intensity of the long-wavelength UV absorption of Id in water (ε = 3980 ± 100, λ_{max} = 340 nm) and the corresponding band for a model compound, 4-nitro-1-methylimidazo[4,5-c]pyridin-2-one (Ib) (ε = 5490 ± 100, λ_{max} = 342 nm), in which the nitro group does not experience steric hindrance, indicates twisting of the nitro group relative to the $C_{(4)}$—N bond and, using the data of Braude and Timmons [9], permits us to calculate the rotation angle (32 ± 2° at 25°C).

Imidazolone IIa and its 1,3-dimethyl derivative IId are recovered unaltered upon heating at reflux with excess KOH in water or methanol over 3-5 h and are also not hydrolyzed by hydrochloric acid. However, the action of potassium cyanide, thiourea, hydrazine hydrate, or aniline leads to replacement of the chlorine atom in IId by a cyano, mercapato, hydrazino, or phenylamino group to give IVa-d. 1,3-Dimethyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (IVe) was obtained by the elimination of the chlorine atom upon heating chloride IId with hydriodic acid. However, we should note that the conversion of IId into base IVe is not always reproducible. The reason for this lack of reproducibility is unknown. Base IVe may also be obtained by the desulfuration of thione IVb with dilute nitric acid. Especially high and stable yields of base IVe were achieved upon the oxidative elimination of the hydrazino group in IVc using azobenzene at 170°C. In this case, azobenzene is reduced to hydrobenzene.



IV a– e

IV a X = CN; b X = SH; c X = NHNH$_2$; d X = C$_6$H$_5$NH; e X = H

EXPERIMENTAL

The PMR spectra were taken on a Tesla 467 spectrometer in CF_3CO_2H at 60 MHz with TMS as the internal standard. The UV spectra were taken on a Spectromom 204 spectrometer in water. The concentration of the solutions was 10^{-4} mole/liter. Derivatives Ia-d were obtained according to our previously published procedures [1].

The elemental analysis of these products for C, H, N, and Cl were in accord with their calculated values.

7-Bromo-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (III, $C_6H_4N_3BrO$). A mixture of 5.64 g (30 mmoles) 5-bromo-3,4-diaminopyridine [7] and 3.6 g (60 mmoles) urea was fused for 1 h at 175-180°C. The solidified mass was triturated, stirred with 20 ml water, and filtered. Reprecipitation from solution in 5% alkali by adding hydrochloric acid gave 6 g (93.4%) light gray prisms with mp 376-377°C.

4-Nitro-7-bromo-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (Ie, $C_6H_3BrN_4O_3$). A solution of 5.35 g (25 mmoles) base III in 15 ml concentrated sulfuric acid was poured into a solution of 7 g (69 mmoles) potassium nitrate in 15 ml concentrated sulfuric acid with ice cooling. The mixture was heated for 2 h at 100°C, cooled, poured onto ice, and neutralized by the addition of aqueous ammonia to pH 6. The precipitate was filtered off, washed with cold water, and dried to give 5.8 g (90%) Ie. Recrystallization from dimethylsulfoxide gave prisms with mp 352-353°C.

4-Nitro-7-bromo-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (If, $C_8H_7BrN_4O_3$). A sample of 5.9 ml (7.98 g, 63 mmoles) dimethyl sulfate was added to a solution of 5.2 g (20 mmoles) nitro compound Ie in 42 ml 7.5% aq. NaOH at a rate such that the reaction temperature did not exceed 33-35°C. After 10-15 min, the solution turned from bright crimson to yellow and a light yellow precipitate formed. The mixture was stirred for 1 h at room temperature and an additional 3 ml (4 g, 31 mmoles) $(CH_3)_2SO_4$ was added. This mixture was maintained for 0.5 h and 10 ml 7.5% aq. NaOH was added. The precipitate was filtered off, washed with water, and dried to give 4.4 g (76%) bright yellow prisms with mp 185-186°C (from dioxane).

4-Chloro-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (IIa). A mixture of 1 g (5.5 mmoles) nitro compound Ia and 20 ml concentrated hydrochloric acid was heated in a sealed glass ampule at 150-160°C for 10-12 h. The ampule contents were evaporated to dryness. The residue was dissolved in 5-7 ml water and brought to pH 6 by the addition of aqueous ammonia. The precipitate was filtered off, washed with a minimal amount of cold water, and purified by reprecipitation from solution in a mixture of one part hydrochloric acid and three parts water by the addition of ammonia. The yield of IIa was 0.61 g (70%). Product IIa was obtained as colorless prisms with mp 342°C (after reprecipitation from solution in 5-10% hydrochloric acid by adding ammonia) and was identical to a sample obtained in our previous work [6].

Products IIb and IIe were obtained under the same conditions from nitro compounds Ib and Ie (see Table 1).

4-Bromo-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (IIg) was obtained by an analogous procedure from 2 g (11 mmoles) Ia in 20 ml 48% hydrobromic acid. The yield of IIg was 1.9 g.

4-Bromo derivatives IIh and IIk were synthesized by analogy from nitro compounds Ib and Ie.

4-Chloro-3-methyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (IIc). A mixture of 1 g (5 mmoles) nitro compound Ic in 20 ml concentrated hydrochloric acid was heated at reflux for 5-6 h. In a variant of this procedure, the mixture was heated in the presence of 0.5-0.6 g urea. The reaction product was isolated as described for IIa. The yield of IIc was 0.75 g.

Analogous procedures gave chlorides IId and IIf from Id and If. Heating the same starting compounds with 48% hydrobromic acid gave bromides IIi, IIj, and II*l*.

4-Fluoro-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (IIm). A mixture of 2.1 g (10 mmoles) nitro compound Id, 20 ml 42% hydrofluoric acid, and 1.2 g (20 mmoles) urea was heated at reflux for 6 h in a 50-ml Ftoroplast-4 cylinder equipped with a Teflon-lined condenser. The reaction product was separated by analogy to the above procedure. The yield of IIm was 1.2 g (67%).

Attempt to Replace the Nitro Group by a Halogen Atom in 5-Nitro-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one. A mixture of 1 g (5.5 mmole) 5-nitro-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one [8] and 20 ml concentrated hydrochloric acid or 48% hydrobromic acid was heated in a sealed glass ampule for 12 h at 180-190°C. A sample of 0.65 g (11 mmoles) urea was added to the reaction mixture in a parallel experiment. After evaporation of the reaction mixture, the residue was mixed with 3-5 ml water and neutralized by adding aqueous ammonia. The precipitate was filtered off and dried to give 0.99 g starting compound. The melting point of a mixture of the sample recovered and the starting compound was undepressed. The IR spectra of the sample recovered and the starting compound were identical.

A similar result was obtained upon heating 5-nitro-1,3-dimethylimidazo[4,5-c]pyridin-2-one [8] with concentrated hydrochloric acid and hydrobromic acids.

Attempt to Replace the Chlorine Atom by a Hydroxyl Group in IIa and IId. A. A solution of 0.5 g (3 mmoles) chloride IIa in 20 ml 10% aqueous or methanolic KOH was heated at reflux for 5 h. After cooling, the alkaline mixture was carefully neutralized by adding concentrated hydrochloric acid and the precipitate was filtered off. When methanol was present in the mixture, it was distilled off after neutralization. Then, 8 ml water was added and the precipitate was filtered off. Reprecipitation from a weakly acidic solution by adding ammonia gave 0.45 g IIa and the melting point of a mixture of the recovered sample and the starting compound was undepressed. Analogously, base IId remained unchanged after heating with aqueous or methanolic KOH under the same conditions.

B. A mixture of 0.5 g chloride IId and 20 ml hydrochloric acid or 98-99% formic acid was heated at reflux for 5 h. The solution was evaporated to dryness. The residue was dissolved in 5 ml water and ammonia was added to bring the pH to 6. The crystalline precipitate (0.4 g) was filtered off. The recovered sample was identical to the base IId.

4-Cyano-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (IVa, $C_9H_8N_4O$). A mixture of 5 g (25 mmoles) chloride IId and 1.9 g (30 mmoles) potassium cyanide in 30 ml dimethylsulfoxide was heated at reflux for 10 h. The solvent was distilled off in vacuum to leave a dry residue, which was extracted with four 10-ml hot benzene portions. The extract was evaporated to give 3.5 g (74%) Va as needles with mp 234-235°C (from dioxane).

4-Mercapto-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (IVb, $C_8H_9N_3O$). A mixture of 2 g (10 mmoles) IId, 2.5 (33 mmoles) thiourea, and 30 ml ethanol was heated in a sealed glass ampule for 4 h at 150-160°C. The ampule contents were evaporated to dryness. The residue was mixed with 20 ml water. The precipitate was filtered off and dried to give 1.5 g (79%) IVb, mp 308-310°C (after reprecipitation from solution in 5% aq. NaOH by adding hydrochloric acid).

4-Hydrazino-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (IVc, $C_8H_{11}N_5O$). A mixture of 2 g (10 mmoles) IId and 10 ml (0.2 mole) 98% hydrazine hydrate was heated at reflux for 4 h. The precipitate formed upon cooling was filtered off, pressed firmly, and dried to give 1.85 g (96%) IVc as long crystals with mp 184-185°C (from ethanol).

4-Phenylamino-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (IVd, $C_{14}H_{14}N_4O$). A mixture of 1 g (5 mmoles) 4-chloro-1,3-dimethylimidazo[4,5-c]pyridin-2-one (IId) and 0.93 g (10 mmoles) freshly distilled aniline was fused at 150-155°C for 2 h. The solidified mass obtained upon cooling was ground and mixed with 5 ml water. A light violet precipitate was obtained. Water (3 ml) was added to the precipitate and the mixture was brought to pH 10 by adding aqueous ammonia. The precipitate was filtered off, washed with a minimal amount of cold water and dried to give 1.1 g (86%) IVd. Recrystallization from benzene gave prisms with a violet hue, mp 130-131°C.

1,3-Dimethyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (IVd, $C_8H_9N_3O$). A. A mixture of 3 g (15 mmoles) chloride IId, 0.7 g (0.023 mole) red phosphorus, and 30 ml hydriodic acid (molar mass 1.5) was heated at reflux for 12 h. The solution was evaporated to a third of the original volume. The residue was made highly basic by the addition of 20% aq. NaOH. A light yellow, viscous oil separated out, which crystallized upon standing. The yield of IVe was 2.2 g (90%), mp 103-106°C (from hexane).

B. A mixture of 2 g (10 mmoles) IVb and 40 ml 10% nitric acid was carefully heated on a water bath. When the bath temperature reached 75°C, the mixture began to bubble. The rapid release of nitrogen oxides and dissolution of the solid were observed. The solution was maintained for 1 h at 75-80°C and evaporated to dryness. The residue was dissolved in 10 ml water and brought to pH 10 by the addition of 20% aq. NaOH. The reaction product was extracted with five 10-ml portions of hot benzene. The extract was dried over anhydrous Na_2SO_4 and the solvent was distilled off to give 1.2 g (74%) colorless crystals with mp 102-103°C (from hexane).

C. A mixture of 1.93 g (10 mmoles) IVc and 2 g (11 mmoles) azobenzene was heated for 1 h at 170°C. Nitrogen was evolved and the mixture became homogeneous. The solidified mass obtained upon cooling was triturated, washed with five 10-ml portions of hot water, and extracted with four 10-ml chloroform portions from aqueous solution. The extract was dried over Na_2SO_4. The solvent was distilled off to give 1.6 g (100%) IVc as violet crystals, mp 103-104°C (from hexane). The melting points of mixed samples of this product with the samples obtained by procedures A and B were not depressed. The PMR spectra of all three samples were identical.

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