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2-FORMYLIMIDAZO[4,5-b]-AND 2-FORMYLIMIDAZO[4,5-c]PYRIDINES

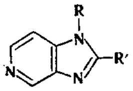
Yu. M. Yutilov and L. I. Kovaleva

UDC 547.781/785.5 : 542.943

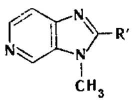
The corresponding aldehydes were obtained by oxidation of N-substituted 2-methylimidazo-[4,5-b]- and 2-methylimidazo[4,5-c]pyridines with selenium dioxide. Some of their properties and transformations were studied.

The preparation of unsubstituted 2-formylimidazo[4,5-b]pyridine and 2-formylimidazo[4,5-c]pyridine from 2,3- and 3,4-diaminopyridines and ethyl diethoxyacetate was described in [1].

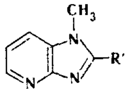
The present paper is devoted to the preparation of N^1- and N^3-substituted 2-formylimidazo[4,5-b]-pyridines and 2-formylimidazo[4,5-c]pyridines (I-III, XII, XVII, XIX, and XX) and to a study of some of their transformations with participation of the aldehyde group.



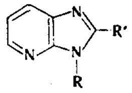
I-XI



XII-XVI



XVII, XVIII



XIX-XXVI

I R=CH_3, R'=CHO; II, XIX R=$CH_2C_6H_5$, R'=CHO; III, XX R=C_6H_5, R'=CHO; IV R==R'=CH_3; V, XXI R=$CH_2C_6H_5$, R'=CH_3; VI, XXII R=C_6H_5, R'=CH_3; VII R=CH_3, R'=CH=CHCOOH; VIII R=CH_3, R'=CN; IX, XXIV R=$CH_2C_6H_5$, R'=CN; X R=CH_3, R'=$CONH_2$; XI R=$CH_2C_6H_5$, R'=$CONH_2$; XII, XVII R'=CHO; XIII, XVIII R'=CH_3; XIV R'=CH=CHCOOH; XV R'=CN; XVI R'=$CONH_2$; XXIII R=C_6H_5, R'=CH==CHCOOH; XXV R=C_6H_5, R'=CN; XXVI R=C_6H_5, R'=$CONH_2$

Aldehydes I-III, XII, XVII, XIX, and XX were prepared by oxidation of 2-methylimidazopyridines (IV-VI, XIII, XVIII, XXI,and XXII) with selenium dioxide as in [2, 3]. The reaction was carried out in toluene, dioxane, aqueous dioxane, water, trifluoroacetic acid, and acetic anhydride; in the last two solvents the oxidation proceeds extremely slowly. The best results were achieved when dioxane was used as the solvent [4]. The action of an equivalent amount of selenium dioxide on bases IV and XIII gives, in addition to aldehydes I and XII, a certain amount (up to 18%) of 2-unsubstituted 1-methyl-1H- and 3-methyl-3H-imidazo-[4,5-c]pyridines; this may be associated with the more extensive oxidation of the starting compounds to the corresponding 2-carboxylic acids and their subsequent decarboxylation under the reaction conditions.

Aldehydes of the c series (I-III and XII) tend to add water to give monohydrates that are completely stable at room temperature and have IR spectra (KBr pellets) that do not contain carbonyl absorption. Carbonyl absorption can be observed in CCl_4 solution at 1705-1720 cm^{-1} after vacuum drying of the sample at 105-110° (5-10 mm) for 2 h. These results constitute evidence for the ability of aldehydes I-III and XII to

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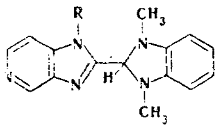
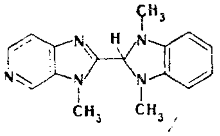
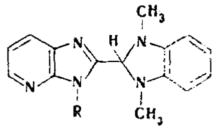
TABLE 1. 2-Formylimidazo[4,5-b] and 2-Formylimidazo[4,5-c]-pyridines and Their Derivatives

Compound	mp, °C (crystallization solvent)	Empirical formula	Found, %			Calc., %			Yield, %
			C	H	N	C	H	N	
I	172 (water)	$C_8H_7N_3O \cdot H_2O$	53,2	5,1	23,8	53,6	5.1	23,4	75
Oxime	238 (alcohol)	$C_8H_8N_4O$	54,4	4,9	31.9	54,5	4.6	31,8	86
Phenylhydrazone	198—199 (alcohol–benzene)	$C_{14}H_{13}N_5$	66,7	5,5	28,3	66,9	5,2	27,9	80
4-Nitrophenylhydrazone	261—262 (alcohol–benzene)	$C_{14}H_{12}N_6O_2$	56,5	3,9	28,1	56,8	4,1	28,4	88
2,4-Dinitrophenylhydrazone	308 (alcohol–benzene)	$C_{14}H_{11}N_7O_4$	49,6	3,6	28,9	49,3	3.2	28,7	88
Isonicotinoylhydrazone	288 (alcohol)	$C_{14}H_{12}N_6O$	60,0	4,4	30,3	60.0	4,3	30,0	60
II	99—100 (water)	$C_{14}H_{11}N_3O \cdot H_2O$	66,3	5,3	16,7	65,9	5,1	16,5	84
Oxime	230 (methanol)	$C_{14}H_{12}N_4O$	66,5	4,9	22,5	66,7	4.8	22,2	80
Isonicotinoylhydrazone	185 (alcohol–ether)	$C_{20}H_{16}N_6O$	67,5	4,4	23,9	67,4	4,5	23,6	63
III	125 (water)	$C_{13}H_9N_3O \cdot H_2O$	64,9	4,6	17,2	64,7	4,6	17,4	50
Oxime	192—193 (alcohol)	$C_{13}H_{10}N_4O$	65,8	4,4	23,8	65,5	4,2	23,6	90
XII	178 (water)	$C_8H_7N_3O \cdot H_2O$	53,9	5,1	23,2	53,6	5,1	23,4	50
Oxime	275 (pyridine)	$C_8H_8N_4O$	54,2	4,7	31,6	54,5	4,6	31,8	85
4-Nitrophenylhydrazone	310 (dioxane)	$C_{14}H_{12}N_6O_2$	56,6	4,0	28,6	56,8	4,1	28,4	83
2,4-Dinitrophenylhydrazone	304 (alcohol–benzene)	$C_{14}H_{11}N_7O_4$	49,1	3,4	28,9	49,3	3,2	28,7	75
Isonicotinoylhydrazone	258 (alcohol)	$C_{14}H_{12}N_6O$	59,8	4,2	29,9	60,0	4,3	30,0	70
XVII	176 (benzene–hexane)	$C_8H_7N_3O$	59,3	4,2	26,4	59,6	4,4	26,1	56
Oxime	237—238 (alcohol)	$C_8H_8N_4O$	54,7	4,5	31,9	54,5	4,6	31,8	79
4-Nitrophenylhydrazone	282—283 (alcohol–benzene)	$C_{14}H_{12}N_6O_2$	56,6	4,3	28,7	56,8	4,1	28,4	80
Isonicotinoylhydrazone	294 (alcohol)	$C_{14}H_{12}N_6O$	59,9	4,2	30,3	60,0	4,3	30,0	68
XIX	99—100 (benzene–hexane)	$C_{14}H_{11}N_3O$	70,7	4,8	17,9	70,9	4,7	17,7	70
Oxime	249—250 (methanol)	$C_{14}H_{12}N_4O$	66,5	4,9	22,4	66,7	4,8	22,2	65
4-Nitrophenylhydrazone	244 (alcohol)	$C_{20}H_{16}N_6O_2$	64,6	4,5	22,9	64,5	4,3	22,6	90
XX	134—136 (benzene–hexane)	$C_{13}H_9N_3O$	70,1	4,2	18,9	69,9	4,1	18,8	80
Oxime	246—247 (alcohol)	$C_{13}H_{10}N_4O$	65,3	4,3	23,7	65,5	4,2	23,5	64
4-Nitrophenylhydrazone	245 (alcohol)	$C_{19}H_{14}N_6O_2$	63,5	3,9	23,7	63,7	3,9	23,5	83

undergo covalent hydration of the carbonyl group with conversion of it to a gem-dihydroxymethyl group. Aldehydes of the b series (XVII, XIX, and XX) do not form hydrates, and their IR spectra contain intense carbonyl bands at 1700-1710 cm^{-1} (KBr pellets). In a chemical respect, all of the aldehydes under consideration behave similarly and display properties characteristic for them, forming oximes, hydrazones and undergoing condensation reactions. Thus aldehydes I, XII, and XX are converted to the corresponding acrylic acids (VII, XIV, and XXIII) when they are heated with malonic acid in the presence of piperidine.


XXVII, XXVIII


XXIX


XXX, XXXI

XXVII R = CH$_3$; XXVIII, XXXI R = CH$_2$C$_6$H$_5$; XXX R = C$_6$H$_5$

Similar 2-substituted dihydrobenzimidazoles (XXVII-XXXI) [5] were obtained by brief heating of the aldehydes with N,N'-dimethyl-o-phenylenediamine in pyridine solution.

The oximes of aldehydes I-III, XII, XIX, and XX can be easily dehydrated by means of acetic anhydride to nitriles VIII, IX, XV, XXIV, and XXV ($\nu_{C \equiv N}$ 2245-2258). As in [6], saponification of the nitriles in concentrated sulfuric acid solution at room temperature gives the corresponding imidazopyridine-2-carboxamides (X, XI, XVI, and XXVI) (Table 3) in high yields.

TABLE 2. β-(Imidazopyridine-2-yl)acrylic Acids and 2-(1',3'-Dimethyl-2',3'-dihydrobenzimidazol-2'-yl)imidazopyridines

Compound	mp, °C*	Empirical formula	Found, %			Calc., %			Yield, %
			C	H	N	C	H	N	
VII	280	$C_{10}H_9N_3O_2$	58,8	4.6	20.9	59,1	4.5	20,7	55
XIV	262—263	$C_{10}H_9N_3O_2$	59,3	4.7	20.9	59,1	4.5	20.7	60
XXIII	271—272	$C_{15}H_{11}N_3O_2$	67.7	4.3	16.0	67,9	4.2	15,8	43
XXVII	228	$C_{16}H_{17}N_5$	68,5	6.2	25,3	68,8	6,1	25,1	55
XXVIII	225	$C_{22}H_{21}N_5$	74,2	5,8	19,9	74,3	6,0	19.7	50
XXIX	244	$C_{16}H_{17}N_5$	68,7	6,3	25,3	68,8	6,1	25,1	60
XXX	282—284	$C_{21}H_{19}N_5$	73,7	5,7	20,8	73,9	5,6	20,5	60
XXXI	209—211	$C_{22}H_{21}N_5$	74,1	5.6	19,5	74,3	6,0	19,7	60

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*Compounds VII and XIV were crystallized from water, XXIII was crystallized from alcohol, and the remaining compounds were crystallized from dioxane.

TABLE 3. 2-Cyano and 2-Carbamoyl Derivatives of Imidazo[4,5-b]- and Imidazo[4,5-c]pyridine

Compound	mp, °C*	Empirical formula	Found, %			Calc., %			IR spectra, cm^{-1} (KBr pellets)	Yield, %
			C	H	N	C	H	N		
VIII	187	$C_8H_6N_4$	60,7	3,9	35,6	60,8	3,8	35,4	$\nu_{C\equiv N}$ 2254	83
IX	132	$C_{14}H_{10}N_4$	72,1	4,5	24,2	71,8	4,3	23,9	$\nu_{C\equiv N}$ 2258	65
X	260	$C_8H_8N_4O$	54,3	4,4	31,8	54,5	4.6	31,8	$\nu_{C=O}$ 1710; δ_{N-H} 1700 ν_{N-H} 3390, 3455	82
XI	234	$C_{14}H_{12}N_4O$	66,5	5,1	22,4	66,7	4,8	22.2	$\nu_{C=O}$ 1705 ν_{N-H} 3300, 3400	60
XV	153—154	$C_8H_6N_4$	60,7	3.9	35,6	60,8	3,8	35,4	$\nu_{C\equiv N}$ 2255	84
XVI	275	$C_8H_8N_4O$	54,2	4,4	31,7	54,5	4,6	31,8	$\nu_{C=O}$ 1695; δ_{N-H} 1670 ν_{N-H} 3222, 3360	80
XXIV	107—108	$C_{14}H_{10}N_4$	71,6	4,5	24.1	71,8	4,3	23.9	$\nu_{C\equiv N}$ 2245	82
XXV	151—152	$C_{13}H_8N_4$	70,8	3,9	25,5	70,9	3,7	25,4	$\nu_{C\equiv N}$ 2245	93
XXVI	203—204	$C_{13}H_{10}N_4O$	65,4	4,3	23,6	65,5	4,2	23,5	$\nu_{C=O}$ 1710 ν_{N-H} 3420, 3460	74

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*Compounds VIII, XV, XXIV, and XXV were crystallized from benzene; IX was crystallized from benzene–hexane; and X, XI, XVI, and XXVI were crystallized from methanol.

TABLE 4. IR Spectra of the Aldehydes

Compound	IR spectrum, ν_{CO}, cm^{-1}	
	KBr	CCl_4
I	—	1720
II	—	1703
III	—	1720
XII	—	1712
XVII	1700	1715
XIX	1700	1715
XX	1710	1720

EXPERIMENTAL

The IR spectra were recorded with a UR-20 spectrometer. The previously undescribed V, XIII, XXI, and XXII were obtained by the method used to prepare IV, VI, and XVIII [7-9].

2,3-Dimethyl-3H-imidazo[4,5-c]pyridine (XIII). A mixture of 5 mmole of 4-amino-3-methylaminopyridine, 15 mmole of acetic anhydride, and 25 mmole of glacial acetic acid was heated at 160-170° for 1 h, after which the excess acetic acid and its anhydride were removed by vacuum distillation, and the residue was dissolved in the minimum volume of water. The aqueous solution was made strongly alkaline with concentrated KOH solution and extracted with benzene. The extract was dried with solid alkali, and the solvent was removed by distillation to give a product with mp 145° (from benzene) in 90% yield. Found: C 65.3; H 6.4%. $C_8H_9N_3$. Calculated:. C 65.3; H 6.2%.

1-Benzyl-2-methyl-1H-imidazo[4,5-c]pyridine (V). This compound, with mp 124° (from benzene–hexane), was obtained in 77% yield from 3-amino-4-benzylaminopyridine [10] as in the preceding experiment. Found: C 75.2; H 5.5%. $C_{14}H_{13}N_3$. Calculated: C 75.3; H 5.9%.

3-Benzyl-2-methyl-3H-imidazo[4,5-b]pyridine (XXI). This compound, with mp 94-95° (from hexane), was obtained in 90% yield from 3-amino-2-benzylaminopyridine [11] as described above. Found: C 75.5; H5.9%. $C_{14}H_{13}N_3$. Calculated: C 75.3; H 5.9%.

3-Phenyl-2-methyl-3H-imidazo[4,5-b]pyridine (XXII). This compound, with mp 77-78° (from hexane), was obtained in 60% yield from 3-amino-2-phenylaminopyridine [12]. Found: C 74.6; H 5.6%. $C_{13}H_{11}N_3$. Calculated: C 74.6; H 5.3%.

2-Formylimidazo[3,5-b]- and 2-Formylimidazo[4,5-c]pyridines (I-III, XII, XVII, XIX, XX, Table 1). A 10-mmole sample of freshly sublimed selenium dioxide was added in portions at 70-80° to a solution of 10 mmole of 2-methylimidazopyridine (IV-VI, XIII, XVIII, XXI, and XXII) in 30-40 ml of dioxane, after which the mixture was refluxed for 2 h, and the selenium was removed by filtration. The solvent was removed by distillation in a stream of carbon dioxide, and the residue was crystallized from an appropriate solvent.

The mother liquors after the first recrystallization of aldehydes I and XII from water were acidified to pH 2 with concentrated HCl and evaporated to dryness. The residue was made alkaline with excess concentrated alkali solution, and the liberated oil was extracted with benzene. The solvent was removed from the extract by distillation to give 15-18% of 1-methyl-1H-imidazo[4,5-c]pyridine with mp 112° (from benzene) and 3-methyl-3H-imidazo[4,5-c]pyridine with mp 101° (from benzene). According to the data in [13], these compounds have mp 112.5 and 101-101.5°, respectively.

β-(Imidazopyridin-2-yl)acrylic Acids (VII, XIV, and XXIII, Table 2). A mixture of 1 mmole of aldehyde (I, XII, or XX), 2 mmole of malonic acid, 0.2 ml of pyridine, and 0.05 ml of piperidine was heated on an oil bath at 125-130° for 30 min, after which it was cooled, and the melt was dissolved in 1 ml of water. The aqueous solution was acidified to pH 3 with 10% HCl solution, and the resulting precipitate was removed by filtration and washed with water.

2-(1',3'-Dimethyl-2',3'-dihydrobenzimidazol-2'-yl)imidazopyridines (XXVII-XXXI, Table 2). A mixture of 1 mmole of aldehyde, 1.1 mmole of N,N'-dimethyl-o-phenylenediamine, and 2 ml of dry pyridine was refluxed for 5-10 min, after which it was cooled, and the resulting precipitate was removed by filtration and washed with alcohol.

2-Cyanoimidazopyridines (VIII, IX, XV, XXIV, and XXV, Table 3). A solution of 1 mmole of the oxime of the corresponding aldehyde in 2 ml of acetic anhydride was refluxed for 7 h, after which the excess anhydride was removed by distillation, and the residue was dissolved in water. The aqueous solution was made alkaline to pH with sodium carbonate solution, and the resulting precipitate was removed by filtration, washed with water, and dried.

2-Carbamoylimidazopyridines (X, XI, XVI, and XXVI, Table 3). A 1.5-mmole sample of the 2-cyano derivatives of the imidazopyridine was dissolved in 0.65 ml of cooled (to 5°) concentrated H_2SO_4, and the solution was allowed to stand at room temperature for 48 h, after which 1 g of ice was added, and the mixture was neutralized with potassium carbonate. The resulting precipitate was removed by filtration and washed with water.

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RESEARCH ON IMIDAZO[1,2-a]BENZIMIDAZOLE DERIVATIVES

XI.* SYNTHESIS OF 2-ARYLAMINO DERIVATIVES OF 9-METHYLIMIDAZO[1,2-a]BENZIMIDAZOLE

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and L. G. Nachinennaya

UDC 547.785.5.07

2-Arylamino derivatives of 9-methylimidazo[1,2-a]benzimidazole were obtained by cyclization of the products of the reaction of 2-amino-1-methylbenzimidazole with chloroacetic acid anilides. The former undergo diazo coupling and acetylation in the 3 position of the system, and the amino groups of secondary amines are also acetylated.

The previously unknown 2-arylamino derivatives of 9-methylimidazo[1,2-a]benzimidazole (IIa-e) were synthesized from N-arylamides of 2-imino-1-methyl-3-benzimidazolylacetic acid (Ia-e) by closing of a new imidazole ring through the amide carbonyl group and the imino group.

Only extremely scanty information regarding the synthesis of such amines in a series of condensed imidazole systems is available. The only representative of this class of compounds – 2-acetamidoimidazo-[1,2-a]pyridine – was obtained by heating the tosylimino derivative of 1-carbamoylmethyl-2-pyridoneimine [2] in acetic anhydride. We were unable to obtain unsubstituted 2-amino-9-methylimidazo[1,2-a]benzimidazole by a similar method, inasmuch as we were unable to convert 2-imino-3-carbamoylmethyl-1-methylbenzimidazoline (III) to the tosyl derivative. The action of acetic anhydride on imine III gives initially the N-acetyl derivative, and, as in the case of 3-carboxylmethyl-substituted compounds, 3-acetyl-2,9-dimethylimidazo[1,2-a]benzimidazole [3] is formed on prolonged heating in the presence of anhydrous sodium acetate. The use of phosphorus oxychloride as the condensing agent leads to resinification, possibly as a consequence of the instability of the resulting amino derivative.

As one would expect, we therefore undertook the synthesis of the more stable 2-arylamino-substituted imidazo[1,2-a]benzimidazoles. The starting N-arylamides (Ia-e) were obtained by heating 2-amino-1-methylbenzimidazole with chloroacetic acid anilides in acetone. The cyclization of Ia-e in phosphorus oxychloride proceeds smoothly, and the hydrochlorides (IIa-e) of the 2-arylamino derivatives are formed in 90-95% yields. The IR spectra of the latter do not contain the absorption band of a CO group at 1700-1705 cm^{-1} that is present in the spectra of the starting amides. In the free state, arylamines IIa-e are distinguished by high instability.

The structure adopted for IIa-e is in agreement with the chemical properties manifested by them. Stable diacetyl derivatives Ia, c-e are formed on treatment of secondary amines IIa, c-e (R = H) with acetic anhydride. Acetylation takes place at the amino group and in the 3 position of the three-ring system,

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*See [1] for communication X.

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