NUCLEOPHILIC SUBSTITUTION IN 2-NITRO-3-HALOPYRIDINES

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Nucleophilic substitution occurs in the 2 or 3 position in 2-nitro-3-halopyridines depending on the nature of the halogen and the substituting agent. A series of new 2,3-substituted pyridines were obtained as a result of the reactions.

It is known that the nitro group in 2-nitropyridine and its derivatives can be readily replaced by hydrazine [1], halogen [2], and hydroxy groups [1, 3]. 2-Nitropyridine does not react with ammonia [3]. The ethoxy group in 2-nitro-3-ethoxypyridine is replaced on reaction with ammonia, and 2-amino-3-ethoxypyridine is obtained in 8% yield as a side product [4]. A halogen in the 3 position of pyridine reacts with nucleophiles only under severe conditions [5, 6].

No study of nucleophilic substitution of nitro groups and halogens in the 2 and 3 positions of the pyridine ring, respectively, has been made. In order to accomplish this, we synthesized a number of previously undescribed 2-nitro-3-halopyridines (IIa-c and VIII). 2-Nitro-3-chloro(bromo, iodo)pyridines (IIIa, b, c) were obtained by the Sandmeyer reaction from the previously described [7] 2-nitro-3-aminopyridine (I). It was found that diazotization of pyridine I in the presence of hydrochloric acid brings about not only substitution of the amino group by a chlorine atom but also simultaneous nucleophilic attack at the nitro group, which is replaced by chlorine to give 2,3-dichloropyridine (IIIa). 2,3-Dibromopyridine (IIIb) and 2-nitro-3-bromopyridine (IIb) are obtained in a ratio of 1 : 2 by diazotization of I in hydrobromic acid. If dilute sulfuric acid is introduced into the diazotization reaction, only 2-nitro-3-halopyridines (IIa-c) are isolated in the presence of the corresponding salts. 2-Nitro-3-fluoropyridine (VIII) was obtained by the Schiemann reaction. In contrast to pyridine-3-diazonium tetrafluoroborate [8], 2-nitropyridine-3-diazonium tetrafluoroborate is stable but decomposes at 140°C to give VIII.

Nucleophilic substitution in 2-nitro-3-halopyridines (IIa-c and VIII) has been investigated in reactions with ammonia, morpholine, hydrazine, aniline, and hydrochloric and hydrobromic acids.

It has been established that the labilities of the nitro group and the halogens are commensurable in the reaction of IIa-c with ammonia and morpholine. Products of substitution of both the nitro group and the halogens were obtained for each nucleophile. Thus 2-nitro-3-aminopyridine (V) and 2-amino-3-chloro-(bromo, iodo)pyridines (VIIa-c) were isolated in the reaction of pyridines IIa-c with ammonia, while 2-nitro-3-morpholinopyridine (V) and 2-morpholino-3-chloro(bromo)pyridines (VIIa, b) are formed from IIa, b and morpholine. In the case of pyridine IIc, only 2-nitro-3-morpholinopyridine (V) was obtained on reaction with morpholine.

Compounds IIa, b react differently with benzylamine. Two products – 2-nitro-3-benzylaminopyridine (V) and 2,3-dibenzylaminopyridine (IV) – were also isolated in this case. Compound V (R = benzylamino) was the only compound obtained from IIc in this reaction. (See scheme on following page.)

Products of substitution of only the nitro group were isolated in the reaction of IIa-c with hydrazine. The 2-hydrazino-3-halopyridines (Xa-c) obtained give the characteristic (for 2-hydrazinopyridine) cyclization reaction with nitrous acid and acetic acid to give the corresponding tetrazolo[1,5-a]pyridines (XI) and

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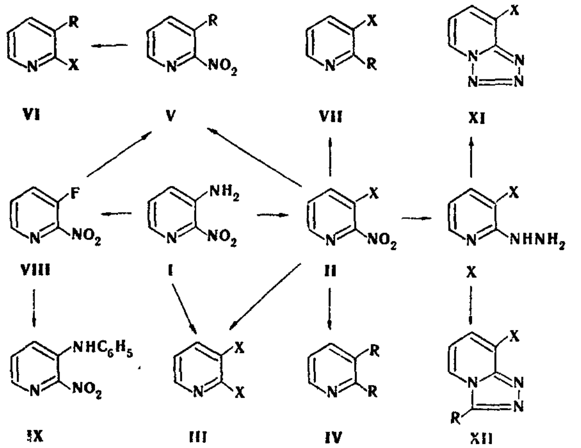

X a=Cl, b=Br, c=I; II X=a, b, c; III X=a, b; IV R=$NHCH_2C_6H_5$; V R=morpholino, NH_2, $NHCH_2C_6H_5$; VI X=a, b, R=morpholino; VII X=a, b, c; R=NH_2, morpholino; X X=a, b, c; XI X=a, b, c; XII X=c; R=CH_3, C_6H_5

sym-triazolo[4,3-a]pyridines (XII). Compounds Xa-c readily give hydrazones, which are converted to triazoles XII on oxidation with bromine.

The nitro group in pyridines IIa-c and V (R = morpholino) is readily replaced by halogen when the compounds are refluxed in hydrochloric or hydrobromic acid. In this case, 2,3-dihalopyridines IIa, b are formed from IIa, b, while products VIa, b – isomers of VIIa, b – are obtained from V (R = morpholino).

2-Nitro-3-fluoropyridine (VIII) reacts with morpholines, benzylamine, and ammonia at room temperature to give fluorine-substitution products (V). In contrast to the chloro, bromo, and iodo derivatives (IIa-c), which do not react with aniline even on refluxing in excess aniline, fluoro derivative VIII readily reacts with aniline even at room temperature to give 2-nitro-3-phenylaminopyridine (IX).

Thus a preparative method for the synthesis of a series of new or previously difficult-to-obtain 2,3-substituted pyridine derivatives, which are of independent interest or are starting materials for subsequent syntheses, was developed by means of nucleophilic substitution in 2-nitro-3-halopyridines (IIa-c and VIII).

EXPERIMENTAL

2-Nitro-3-chloro(bromo, iodo)pyridines (IIa-c). These compounds were obtained as follows: a) from pyridine I via the Sandmeyer reaction in sulfuric acid with crystallization of the resulting nitrohalo derivatives from 50% aqueous alcohol (Table 1),* b) (for pyridine IIb) by diazotization of I in 20% HBr. The yield was 65%.

2,3-Dichloro(dibromo)pyridines (IIIa, b). Compound IIIa was obtained by the Sandmeyer reaction in 25% HCl and was isolated by alkylation of the reaction mixture to pH 7-8 and steam distillation of the reaction product. The yield of product with mp 66-67° (mp 66.5-67.5° [9]) was 65%. Compound IIIb was obtained by the Sandmeyer reaction in 40% HBr. The precipitated IIb was removed by filtration (45% yield). Product IIIb was isolated by dilution of the mother liquor with water (25% yield). The product had mp 58-59° (mp 58.5-59.6° [10]).

2-Nitro-3-fluoropyridine (VIII). This compound was obtained by the method in [8]. The diazonium tetrafluoroborate was decomposed at 140°. Product VIII was extracted from the reaction mixture by means of chloroform. The solvent was evaporated, and the residue was purified by vacuum sublimation at 80-90°. A solution of VIII in chloroform was used without additional purification for the reactions with amines.

Reaction of IIa, b, c with Ammonia. A 1-g (6.0 mmole) sample of pyridine IIa was heated at 150° in 10 ml of 28% ammonium hydroxide for 3 h. The solution was cooled, and the resulting precipitate was recrystallized from petroleum ether to separate 2-amino-3-chloropyridine VIIa from undissolved 2-nitro-3-aminopyridine (V). The yield of VIIa with mp 60-61° (mp 61.5-62° [9]) was 60%. The yield of V was 15%.

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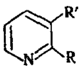
*See Table 1 for the data for the undescribed substances.

TABLE 1. 2,3-Substituted Pyridines



Compound	R	R′	mp, °C	Empirical formula	Found, % C	Found, % H	Found, % N	Calc., % C	Calc., % H	Calc., % N	Yield, %
IIa	NO_2	Cl	90—91	$C_5H_3ClN_2O_2$	37,8	2,00	17,9	37,9	1,9	17,7	55
IIb	NO_2	Br	100—101	$C_5H_3BrN_2O_2$	39,7	1,5	13,6	29,6	1,5	13,8	65
IIc	NO_2	I	98—99	$C_5H_3IN_2O_2$	24,1	1,1	11,1	24,0	1,2	11,2	70
IV	$NHCH_2C_6H_5$	$NHCH_2C_6H_5$	166—167	$C_{19}H_{19}N_3H_2O$	74,2	7,2	13,0	74,3	6,8	13,7	25
V	NO_2	Morpholino	62—63	$C_9H_{11}N_3O_3$	51,5	5,2	20,1	51,7	5,3	20,1	40
V	NO_2	$NHCH_2C_6H_5$	110—111	$C_{12}H_{11}N_3O_2$	62,5	4,9	18,5	62,7	4,8	18,3	15
VIa	Cl	Morpholino	100—101	$C_9H_{11}ClN_2O$	55,1	5,6	14,1	54,4	5,6	14,1	95
VIb	Br	Morpholino	89—90	$C_9H_{11}BrN_2O$	44,3	4,7	11,9	44,5	4,6	11,5	95
VIIa	Morpholino	Cl	94—95	$C_9H_{11}ClN_2O$	54,9	5,8	13,6	54,4	5,6	14,1	40
VIIb	Morpholino	Br	92—93	$C_9H_{11}BrN_2O$	44,5	4,6	11,5	44,5	4,6	11,5	30
VIIc	NH_2	I	87—88	$C_5H_5IN_2$	27,6	2,4	13,0	27,3	2,3	12,7	50
VIII	NO_2	F	38—39	$C_5H_3FN_2O_2$	41,7	2,4	19,9	42,2	2,1	19,7	25
IX	NO_2	NHC_6H_5	85—86	$C_{11}H_9N_3O_2$	61,4	4,4	19,1	61,4	4,2	19,5	55
Xb	$NHNH_2$	Br	147—148	$C_5H_6BrN_3$	32,2	3,4	22,1	31,9	3,2	22,3	55
Xc	$NHNH_2$	I	96—97	$C_5H_6IN_3$	25,7	2,7	17,4	25,5	2,6	17,9	35

Compounds IIb, c react similarly with ammonia to give V ($R = NH_2$) and VIIb, c ($R = NH_2$). The yields of V and VIIb were 15 and 50%, respectively. Compound VIIb had mp 64-65° (mp 64.5-65.5° [10]).

Reaction of Pyridines IIa, b, c with Morpholine. A 1-g (6.0 mmole) sample of IIa was refluxed for 3 h in 10 ml of 50% solution of morpholine in methanol. Water was added to the reaction mixture to precipitate 2-morpholino-3-chloropyridine (VIIa), which was crystallized from 50% aqueous alcohol. The mother liquor was evaporated to dryness, and the residue was recrystallized from 30% aqueous alcohol to give 2-nitro-3-morpholinopyridine (V). The reaction with pyridine IIb was carried out similarly. In the case of IIc, the reaction mixture was evaporated to dryness, and product V (R = morpholino) was crystallized from 30% aqueous alcohol. The yield was 40%.

Reaction of IIa-c with Benzylamine. A 1-g (6.0 mmole) sample of IIa was refluxed for 1 h in 10 ml of a 50% methanol solution of benzylamine. The solvent was evaporated, and the residue was diluted with water and extracted with chloroform. The extract was dried with Na_2SO_4, filtered, and evaporated. The precipitated 2,3-dibenzylaminopyridine (IV) was removed by filtration and crystallized from 50% aqueous alcohol. The reaction was carried out similarly with pyridine IIb. In the case of IIc, a solution in chloroform was evaporated until an oil formed, after which the mixture was treated with ether to give V ($R = NHCH_2C_6H_5$) in 15% yield.

Reaction of Pyridines IIa, b, c with Hydrazine. A 1-g (6.0 mmole) sample of pyridine IIa was refluxed in 10 ml of a 50% solution of hydrazine hydrate in methanol for 1 h or the mixture was allowed to stand at room temperature for 3 h. Evaporation of the reaction mixture precipitated 2 hydrazino-3-chloropyridine (Xa), with mp 160-161° (from water) (mp 160-161° [11]), in 55% yield. Compounds IIb, c were similarly obtained.

Substitution of the Nitro Group in IIa, b and V (R = Morpholino) by Halogen. A 6.0-mmole sample of IIa, b or V (R = morpholino) was refluxed in 10 ml of concentrated HCl or HBr. The reaction products were precipitated with water. Products IIa, b were obtained from IIIa, b, while VIa, b were obtained from V (R = morpholino). Compounds VIa, b were crystallized from 50% aqueous alcohol.

8-Chlorotetrazolo[1,5-a]pyridine (XIa). A 0.5-g (3.5 mmole) sample of pyridine Xa was dissolved in 8 ml of 10% H_2SO_4 and diazotized with 0.8 g (1.1 mmole) of $NaNO_2$ in 2 ml of water. The precipitate was removed by filtration to give 0.48 g (90%) of XIa with mp 182-183° (from water). Found: C 38.9; H 2.0; N 36.0%. $C_5H_3ClN_4$. Calculated: C 38.7; H 1.9; N 36.1%. Compounds XIb, c were similarly obtained. Compound XIb had mp 208-209° (from water). Found: C 29.9; H 1.4; N 27.9%. $C_5H_3BrN_4$. Calculated: C 30.4; H 1.5; N 28.1%. Compound XIc had mp 224-225° (from water). Found: C 24.6; H 1.1; N 22.4%. $C_5H_3IN_4$. Calculated: C 24.4; H 1.2; N 22.8%. Compound XIa in trifluoroacetic acid solution did not give an absorption band corresponding to the frequency of the stretching vibrations of the azide group at 2100-2200 cm^{-1}.

8-Bromo-3-methyl-sym-triazolo[4,3-a]pyridine (XIIb). A 0.7-g (4.0 mmole) sample of Xb was refluxed in 20 ml of acetic acid for 9 h. The acetic acid was then removed by distillation to give 0.68 g (95%) of XIIb with mp 161-162° (from benzene). Found: C 39.8; H 3.1; N 19.2%. $C_7H_6BrN_3$. Calculated: C 39.6; H 2.8; N 19.8%.

8-Bromo-3-phenyl-sym-triazolo[4,3-a]pyridine (XIIb). A solution of 0.75 g (4.0 mmole) of Xb in 10 ml of alcohol was heated for 5 min with 0.7 g (6.6 mmole) of benzaldehyde in 10 ml of alcohol. The mixture was treated with water, and the precipitate was removed by filtration to give 1 g (90%) of benzaldehyde 3-bromo-2-pyridylhydrazone with mp 137-138° (from 50% aqueous alcohol). Found: C 52.3; H 3.7; N 15.1%. $C_{12}H_{10}BrN_3$. Calculated: C 52.2; H 3.6; N 15.2%. A 1-g (3.6 mmole) sample of the hydrazone was dissolved in 6 ml of acetic acid, and 1 g (1.5 mmole) of sodium acetate and 0.8 ml of bromine in 2 ml of acetic acid were added. The mixture was refluxed for 5 min, after which it was poured into 10 ml of water. The resulting oil crystallized on standing. The crystals were removed by filtration to give 0.9 g (90%) of XIIb with mp 175-176° (from water). Found: C 52.6; H 2.9; N 14.9%. $C_{12}H_8BrN_3$. Calculated: C 52.6; H 2.9; N 15.3%.

Reaction of VIII with Amines. A twofold excess of the appropriate amine was added to a solution of VIII in chloroform, and the precipitated amine salt was removed by filtration. The solvent was removed by distillation, and product V was crystallized from an appropriate solvent; IX was crystallized from 50% aqueous alcohol.

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