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HALOGENATION OF IMIDAZO[4,5-c]PYRIDINONES

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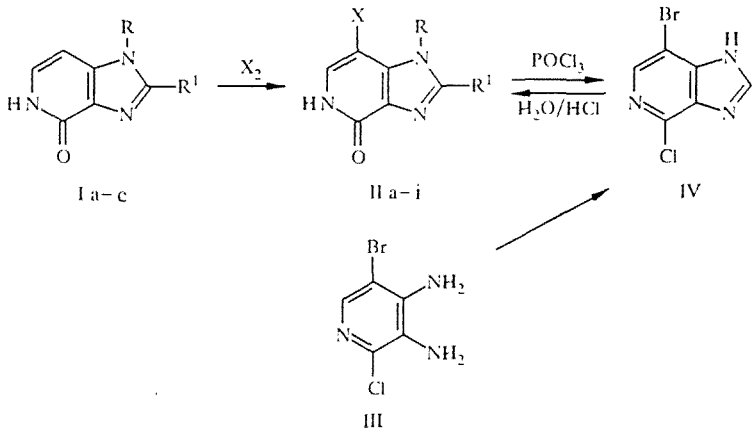
Unsubstituted imidazo[4,5-c]pyridine does not react with chlorine, bromine, or iodine at room temperature or even upon heating to 160°C. The introduction of an oxo group activates the system such that halogenation proceeds readily. Imidazo[4,5-c]pyridin-4-one gives 7-halo derivatives, while imidazo[4,5-c]pyridin-2-ones give 4,7-dihalo products.

Imidazo[4,5-c]pyridine and its 1- and 3-methyl derivatives fail to undergo not only nitration [1] but also bromination. Heating these compounds with bromine in acetic acid at reflux or even in hydrobromic acid at up to 160°C leads only to molecular complexes, which are formed already at room temperature.

We have already shown that the strong activating effect of an oxo group introduced at $C_{(2)}$ of imidazo[4,5-c]pyridine facilitates the nitration of these compounds [1]. With this in mind, we studied the behavior of imidazo[4,5-c]pyridin-4-one (Ia), 2-methylimidazo[4,5-c]pyridin-4-one (Ib), and 2-methylimidazo[4,5-c]pyridin-4-one (Ic) under chlorination, bromination, and iodination conditions. As expected, Ia reacts with an equivalent of bromine at 100°C in acetic acid in the presence of sodium acetate and is converted exclusively into 7-bromo-1H-imidazo[4,5-c]pyridin-4-one (IIb) in yields above 80%. Doubling or tripling the amount of bromine does not lead to the formation of other reaction products. The structure of bromide IIb was established by its convergent synthesis. Cyclization of 2-chloro-5-bromo-3,4-diaminopyridine (III), described in our previous work [2], gave 4-chloro-7-bromoimidazo[4,5-c]pyridine (IV) and hydrolysis of IV upon heating in dilute hydrochloric acid gave IIb. In turn, the product of the bromination of base Ia, namely, IIb, was heated with $POCl_3$ in hydrochloric acid at reflux to give dihalide IV. The PMR spectrum of bromide IIb in CF_3CO_2H has only a singlet at 9.33 ppm assigned to 2-H and a singlet at 7.88 ppm corresponding to 6-H. Bromination of bases Ib and Ic also leads to their 7-bromo derivatives IIe and IIh. Analogously, the chlorination of imidazopyridines Ia-Ic upon heating with sulfuryl chloride in acetic acid gives 7-chloro derivatives IIa, IId, and IIg. The direct action of chlorine on these compounds leads to the formation of a tar, from which no reaction could be isolated or identified.



I a–c II a–i IV III

IIa,d,g X = Cl; IIb,e,f X = Br; IIc,f,i X = I; Ia,c, IIa—c, g-i R = H; Ib, IId-f R = Me; Ic, II g-i R^1 = Me; Ia,b, IIa—f R^1 = H

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TABLE 1. Indices of 7-Haloimidazo[4,5-c]pyridin-4-ones IIa-IIi

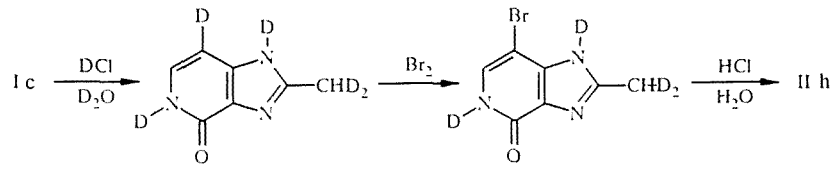
Compound	Chemical formula	T_{mp}, °C*	PMR spectrum, δ, ppm (in CF_3CO_2H)			Yield, %
			1-CH_3, s	2-H, s	6-H, s	
IIa	$C_6H_4ClN_3O$	378...379	—	9.31	7.85	90
IIb	$C_6H_4BrN_3O$	329...330	—	9.33	7.88	83
IIc	$C_6H_4IN_3O$	301...303	—	9.36	8.08	60
IId	$C_7H_6ClN_3O$	266...267	4.51	9.21	7.91	42
IIe	$C_7H_6BrN_3O$	284...285	4.50	9.23	7.86	88
IIf	$C_7H_6IN_3O$	247...248	4.50	9.23	7.95	88
IIg	$C_7H_6ClN_3O$	361...362	—	2.97*[2]	7.77	70
IIh	$C_7H_6BrN_3O$	313...314	—	2.96*[2]	7.86	72
IIi	$C_7H_6IN_3O$	287...288	—	2.97*[2]	7.82	65

*Products IIb and IIc were recrystallized by DMSO, while IId-IIi were recrystallized from water. Chloride IIa was purified by reprecipitation from a solution in 10% hydrochloric acid upon adding ammonia.

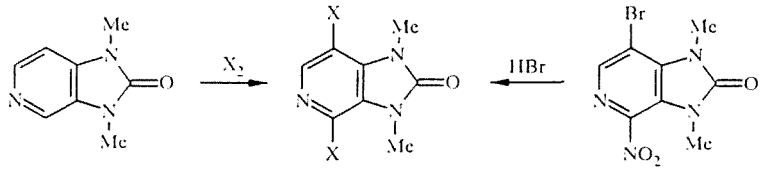
*[2]The signal for 2-CH_3 is a singlet.

The iodination of imidazo[4,5-c]pyridin-4-ones Ia-Ic proceeds smoothly upon the action of iodine in aq. KOH. As in the case of chlorination and bromination, the substitution occurs at $C_{(7)}$ in the pyridine ring (products IIc, IIf, and IIi). The singlet in the PMR spectra of halides Ia and Ic-Ii, corresponding to 6-H, is found at 7.77-7.91 ppm (see Table 1).

We should note the analogy in the halogenation and deuterium exchange reactions of imidazo[4,5-c]pyridin-4-ones Ia-Ic, which may indicate electrophilic substitution in the halogenation reactions. Indeed, heating base Ic with deuterohydrochloric acid at 145-150°C over 10 h gradually gives a product, whose PMR spectrum in DMSO-d_6 has only one aromatic singlet at 7.20 ppm instead of two doublets for vicinal 6-H (7.16 ppm) and 7-H (6.40 ppm) with coupling constant 6.6 Hz in the spectrum of starting base Ic. The signal for the 2-CH_3 group at 3.27 ppm hardly changes position upon deuteration of base Ic but its integral intensity is reduced by a factor of three, indicating the replacement of two hydrogen atoms of the methyl group by deuterium. This permits us to identify the deuteration product of Ic as 7-deutero-2-dideuteromethylimidazo[4,5-c]pyridin-4-one [this should be 2-dideuteromethyl-1(3),5,7-trideuteroimidazo[4,5-c]pyridin-2-one as given in the Experimental and in the formulas on the top of p. 1078!!!] (Id). Thus, the deuterium cation electrophilically replaces the proton at $C_{(7)}$ in starting Ic. Evidence for this conclusion was also found in the bromination of deutero derivative Id carried out analogously to the bromination of Ia-Ic but in deuteroacetic acid, which gave bromide IIj. The PMR spectrum of IIj retains the signal for aromatic proton 6-H (7.23 ppm in DMSO-d_6). The same signal (7.24 ppm) is also found for authentic 7-bromo-2-methylimidazo-[4,5-c]pyridin-4-one (IIh). Heating bromide IIj with hydrochloric acid leads to the complete replacement of its deuterium atoms by hydrogen and the base obtained is completely identical in its indices to bromide IIh.



The halogenation of imidazo[4,5-c]pyridin-2-one proceeds unusually. The bromination of 1,3-dimethyl-1,3-dihydroimidazo[4,5-c]pyridin-2-one (V) in acetic acid at reflux with sodium acetate leads, independently of the amount of bromine introduced, to 4,7-dibromo derivative VIb. The best yield (82%) was obtained with three molar equivalents of bromine relative to base V. The chlorination of V by gaseous chlorine or upon heating this compound with excess sulfuryl chloride proceeds to give 4,7-dichloro-1,3-dimethylimidazo[4,5-c]pyridin-2-one (VIa).

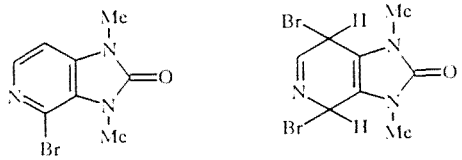


V VI a, b VII

VIa X=Cl; VIbX=Br

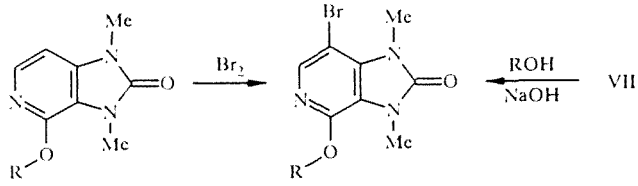
The structure of dibromide VIb was demonstrated by the finding that this derivative is identical to the product of the reaction of 4-nitro-7-bromo-1,3-dimethylimidazo[4,5-c]pyridin-2-one (VII) with hydrobromic acid, in which the nitrogen atom is replaced by a bromine atom [3]. The PMR spectra of halides VIa and VIb (see Table 1) have one singlet for 6-H at 8.43 and 8.52 ppm, respectively, in addition to the signals of the N-methyl groups.

An attempt to obtain dibromide VIb from 4-bromo-1,3-dimethylimidazo[4,5-c]pyridin-2-one (VIII) [3] unexpectedly failed. It proved impossible to introduce a second bromine atom into this molecule even under rather vigorous conditions with excess reagent. The finding that the monosubstitution product is not formed upon the bromination of base V may be evidence for a mechanism involving electrophilic 1,4-addition of the halogen molecule to the diene fragment of the pyridine ring with formation of intermediate IX. Oxidation of molecules with this structure by excess halogen should lead to halides VI. It is not excluded in this case that the failure to brominate monobromide VIII is related to the impossibility of adding a bromine molecule to this compound due to steric hindrance created by the bromine atom already present. However, the situation is fundamentally altered if we go from bromide VIII to other compounds containing an alkoxy group instead of the bromine atom.



VIII IX

In this case, the bromination of Xa and Xb proceeds through electrophilic replacement as in the halogenation of imidazo[4,5-c]pyridin-4-ones Ia-Ic but much more readily. This reaction proceeds in acetic acid at 80-85°C with a stoichiometric amount of bromine and leads to the formation of 7-bromo-4-alkoxy-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-c]-pyridin-2-ones XIa and XIb. The same compounds are readily formed upon heating nitro compounds VII [3] with methanol or ethanol in the presence of alkali as described in one of our previous communications [1].



X a, b XI a, b

Xa, XIa R=Me; Xb , XIb R=Et

EXPERIMENTAL

The PMR spectra were taken on a Tesla 467 spectrometer at 60 MHz in CF_3CO_2H and DMSO-d_6 with TMS as the internal standard. The indices of the synthesized compounds are given in Table 1.

The elemental analysis data for C, H, N, and Hal were in accord with the calculated values.

Attempts to Brominate Imidazo[4,5-c]pyridine and Its 1- and 3-Methyl Derivatives. A. A solution of 0.5 ml (1.6 g, 10 mmoles) bromine in 1 ml acetic acid was added dropwise to a sample of 0.6 g (5 mmoles) imidazo[4,5-c]pyridine and 0.82 g (10 mmoles) sodium acetate in 10 ml glacial acetic acid. A bright orange precipitate formed immediately. This precipitate dissolved upon heating the reaction mixture to reflux. The mixture was heated at reflux for 5 h and the acid was distilled off using a water pump to leave a dry residue. A sample of 5 ml water was added to the residue and the mixture was neutralized by adding aqueous ammonia to pH 7. The light yellow precipitate was filtered off, dried, and crystallized from water. The complex $C_5H_5N_3 \cdot Br_2$ was obtained as prisms with mp 283-285°C (dec.). The yield was 1.1 g (80%).

B. A mixture of the reagents indicated above was heated in a sealed ampule for 5 h at 155-160°C. The reaction product was separated as in procedure A. The product obtained (0.9 g) was identical to the complex obtained in procedure A.

C. A mixture of 0.3 g (2.5 mmoles) imidazo[4,5-c]pyridine, 0.25 ml (0.8 g, 5 mmoles) bromine, and 5 ml 48% hydrobromic acid was heated in a sealed ampule for 3 h at 160°C. After cooling, a light yellow precipitate was filtered off, mixed with 5 ml water and, neutralized by adding aqueous ammonia. The product obtained has mp 282-284°C and does not give a depressed melting point upon mixing with the samples obtained in procedures A and B.

D. A sample of 0.7 g (2.5 mmoles) complex in 20 ml 25% aqueous ammonia was heated at reflux for 10 min. The solution was evaporated to dryness and the residue was crystallized from dioxane to give 0.5 g (83%) of a colorless product, identical to starting imidazo[4,5-c]pyridine in its melting point and PMR spectra.

Analogous results were obtained in the bromination of 1- and 3-methylimidazo[4,5-c]pyridines.

Imidazo[4,5-c]pyridin-4-one (Ia). A solution of 7.7 g (50 mmoles) 4-chloroimidazo[4,5-c]pyridine [4] in 40 ml 85% formic acid was heated at reflux for 7-8 h. Excess formic acid was distilled off in vacuum using a water pump and 15 ml water was added to the residue. The mixture was brought to pH 6 by adding aqueous ammonia. The snow white precipitate was filtered off, washed with water, and dried to give 5.9 g (88%) Ia as needles, mp 356-357°C (from water, mp 320°C [5]).

2-Methylimidazo[4,5-c]pyridin-4-one (Ib, $C_7H_7N_3O$) was obtained as prisms analogously from 8.4 g (50 mmoles) 4-chloro-2-methylimidazo[4,5-c]pyridine [6] and 50 ml 85% formic acid. The yield of Ib was 6.0 g (80%), mp 370°C (from water).

Hydrochloride salt of 1-methylimidazo[4,5-c]pyridin-4-one (Ic, $C_7H_8ClN_3O$) was obtained by heating 15.1 g (90 mmoles) 4-chloro-1-methylimidazo[4,5-c]pyridine [6] in 100 ml 85% formic acid for 5 h with subsequent evaporation of the solution. The residue was heated with 30 ml concentrated hydrochloric acid for 2 h. Hydrochloric acid was evaporated off to leave a dry residue. A sample of 50 ml ethanol was added to the residue and a white precipitate was filtered off to give 15.7 g (94%) Ic as needles with mp 257-258°C (from ethanol).

7-Bromoimidazo[4,5-c]pyridin-4-one (IIb). A. A solution of 1.3 ml (4 g, 25 mmoles) bromine in 2 ml acetic acid was added dropwise to a solution of 2.7 g (20 mmoles) pyridone Ia and 1.64 g (20 mmoles) anhydrous sodium acetate in 30 ml glacial acetic acid. The mixture was heated for 1 h on a steam bath, cooled, and poured onto ice. After neutralization with ammonia, the precipitate formed was filtered off, washed with water, and dried to give 3.55 g (83%) IIb as slightly pink prisms with mp 329-330°C (from DMSO).

The same procedure was used to obtain bromides IIe and IIh from base Ic and hydrochloride Ib (Table 1).

B. A mixture of 0.23 g (1 mmole) IV and 3 ml 20% hydrochloric acid was heated at reflux for 6 h. The solution was evaporated to dryness. A sample of 2 ml water was added to the residue. The solution was brought to pH 7 by adding aqueous ammonia. The precipitate was filtered off, washed with water, and dried to give 0.13 g (62%) IIb, mp 328-329°C. A mixed sample of this product and the product obtained by procedure A gave an undepressed melting point. The PMR spectra of both compounds were identical.

4-Chloro-7-bromoimidazo[4,5-c]pyridine (IV, $C_6H_3BrClN_3$). A. A sample of 0.66 g (3 mmoles) 2-chloro-5-bromo-3,4-diaminopyridine (III) was added to a mixture of 4 ml ethyl orthoformate and 4 ml acetic anhydride. The reaction mixture was heated at reflux for 3 h. The excess reagents were distilled off in vacuum using a water pump. A sample of 3 ml water was added to the residue and the mixture was brought to pH 8 by adding aqueous ammonia. The reaction product was filtered off, dried, and crystallized from 2-propanol to give 0.67 g (97%) IV as light beige prisms with mp 264-265°C.

B. A sample of 0.43 g (2 mmoles) bromopyridone IIb was heated with 4 ml (6.6 g, 43 mmoles) freshly distilled phosphorus oxychloride in a sealed ampule for 7 h at 150°C. Excess $POCl_3$ was distilled off in vacuum using a water pump. The syrupy residue was mixed with ice and neutralized by adding ammonium bicarbonate (to pH 7). The precipitate was filtered off and dried to give 0.35 g (76%) IV. A mixed sample of this product with the product obtained by procedure A did not give a depressed melting point.

7-Chloroimidazo[4,5-c]pyridin-4-one (IIa). A mixture of 1.4 g (10 mmoles) base Ia, 20 ml acetic acid, and 1.2 ml (15 mmoles) sulfuryl chloride was heated on a steam bath for 3 h. The excess reagents were distilled off. A sample of 5 ml ice water was added to the residue and the mixture was brought to pH 6 by adding ammonia. The lilac precipitate was filtered off, washed with water, and dried to give 1.6 g (90%) IIa. Reprecipitation from hydrochloric acid solution by adding ammonia gave a sample with mp 378-379°C.

The corresponding 7-chloro derivatives IId and IIg were obtained from Ib and Ic under the same conditions.

7-Iodoimidazo[4,5-c]pyridin-4-one (IIc). A sample of 0.7 g (5.2 mmoles) base Ia was added to a solution of 1 g (7.2 mmoles) potassium carbonate and, then, 1.3 g (10 mmoles) thoroughly ground iodine was added in portions to the suspension obtained. The mixture was maintained for 1 h at 60°C in a bath and for 1 h at 100°C. The mixture turned from dark lilac to light pink. The reaction mixture was brought to pH 6 by adding hydrochloric acid and the precipitate was filtered off to give 0.81 g (60%) IIc as prisms, mp 301-303°C (from DMSO).

Analogous procedures gave iodides IIf and IIi from IIb and IIc.

2-Dideuteromethyl-1(3),5,7-trideuteroimidazo[4,5-c]pyridin-4-one (Id, $C_7H_2D_5N_3O$). A mixture of 0.75 g (5 mmoles) base Ic and 5 ml concentrated deuterohydrochloric acid was heated in a sealed ampule at 145-150°C for 10 h. The ampule contents were evaporated to dryness. The residue was dissolved in 5 ml D_2O and neutralized by adding potassium carbonate. The light beige precipitate was filtered off, washed with a minimal amount of D_2O, and dried to give 0.65 g (86.6%) Id as prisms with mp 369-370°C (from D_2O). PMR spectrum (DMSO-d_6): 3.27 (1H, s, 2-CHD_2), 7.20 (1H, s, 6-H). A mixed probe with a sample of nondeuterated Ic did not give a depressed melting point.

7-Bromo-2-dideuteromethyl-1(3),5,7-dideuteroimidazo[4,5-c]pyridin-4-one (IIj) was obtained upon bromination of 0.3 g (2 mmoles) deuterated imidazolone Id by the action of 0.2 ml (0.63 g, 3.9 mmoles) bromine in 3 ml CD_3CO_2D as described for nondeuterated imidazolone Ic. The yield of IIj was 0.32 g (70%), mp 313-314°C (from DMSO-d_6).

Heating a sample of 0.15 g (1 mmole) bromoimidazopyridone IIj with 2 ml concentrated hydrochloric acid in a sealed ampule at 120-125°C for 5 h with subsequent evaporation of the solution and making the residue basic by adding aqueous ammonia gave nondeuterated 7-bromo-2-methylimidazo[4,5-c]pyridin-4-one, whose PMR spectrum was identical to the spectrum of bromide IIh.

4,7-Dibromo-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (VIb). A sample of 0.23 ml (0.72 g, 4.5 mmoles) bromine was added to a solution of 0.25 g (1.5 mmole) base V [3] and 0.25 g (3 mmoles) sodium acetate in 5 ml glacial acetic acid and heated at low reflux for 5 h. Excess acid was distilled off. The residue was dissolved in 5 ml water and brought to pH 7 by adding ammonia. The colorless precipitate was filtered off, washed with water, and dried to give 0.4 g (83%) VIb as needles with mp 164°C (from hexane, mp 164°C [3] [sic]).

Heating 0.15 ml (0.47 g, 3 mmoles) bromine and 0.24 g (1 mmole) bromide VIII in 3 ml acetic acid in the presence of 0.16 g (2 mmoles) sodium acetate under analogous conditions gave 0.22 g (91%) starting 4-bromo derivative VIII.

4,7-Dichloro-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (VIa, $C_8H_7Cl_2N_3O$). A. Chlorine obtained from 1 g $KMnO_4$ and 6.2 ml concentrated hydrochloric acid was passed with vigorous stirring through a solution of 0.32 g (2 mmoles) V and 0.16 g (2 mmoles) sodium acetate in 5 ml glacial acetic acid. The solution became turbid and a white precipitate formed. The reaction mixture was heated on a steam bath for 3 h, evaporated to one third initial volume, and brought to pH 7 by adding ammonia. The precipitate was filtered off and dried. Crystallization from hexane gave 0.25 g (54%) VIa as snow white crystals with mp 129-130°C. PMR spectrum (CF_3CO_2H): 3.91 (3H, s, 1-CH_3), 4.00 (3H, s, 3-CH_3), 8.43 (1H, s, 6-H).

B. A mixture of 0.32 g (2 mmoles) imidazolone V and 6 ml (10 g, 74 mmoles) sulfuryl chloride was heated at reflux for 4 h. Excess sulfuryl chloride was distilled off and 2 ml water was added to the residue. Dichloride VIa was isolated as in procedure A. The yield of VIa was 0.15 g (32.3%).

7-Bromo-4-methoxy-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (XIa, $C_9H_{10}BrN_3O_2$). A. A sample of 0.2 ml (0.64 g, 4 mmoles) bromine was added with vigorous stirring to a solution of 0.78 g (4 mmoles) base Xa and 0.4 g (5 mmoles) sodium acetate in 5 ml glacial acetic acid. A bright yellow precipitate formed immediately. The reaction mixture was heated at 80-85°C for 1 h, cooled, poured onto ice, and neutralized by adding ammonia. The colorless precipitate was filtered off, firmly compressed, and dried to give 0.86 g (79%) XIa as needles, which form star-like clumps, mp 139-140°C (from hexane). PMR spectrum (CF_3CO_2H): 3.76 (3H, s, 1-CH_3), 3.91 (3H, s, 3-CH_3), 8.02 (1H, s, 6-H), 4.76 ppm (3H, s, OCH_3).

B. A sample of 0.6 g (2 mmoles) VII [3] was added to a solution of 0.12 g (3 mmoles) NaOH in 6 ml methanol and the mixture was heated at reflux for 3 h. Methanol was evaporated to leave a dry residue and the reaction product was extracted

with hot chloroform. Distillation of the solvent gave 0.54 g (95%) XIa. A sample recrystallized from hexane was mixed with a sample obtained by procedure A. This mixed sample did not give a depressed melting point.

7-Bromo-4-ethoxy-1,3-dimethyl-dihydro-2H-imidazo[4,5-c]pyridin-2-one (XIb, $C_{10}H_{12}BrN_3O_2$). A. Bromide XIb was obtained from 0.4 g (2 mmoles) Xb, 0.2 g (2.4 mmoles) sodium acetate, and 0.1 ml (0.32 g, 2 mmoles) bromine in 5 ml acetic acid by analogy to procedure A for the synthesis of XIa. The yield of XIb was 0.5 g (87%). The product was obtained as long, colorless needles with mp 129-130°C (from hexane). PMR spectrum (CF_3CO_2H): 3.79 (3H, s, 1-CH_3), 3.98 (3H, s, 3-CH_3), 8.09 (1H, s, 6-H), 1.54 (3H, t, CH_3, J = 7.1 Hz), 4.69 ppm (2H, q, O−CH_2, J = 7.1 Hz).

B. Bromide XIb was obtained from 0.12 g (3 mmoles) NaOH and 0.58 g (2 mmoles) nitrobromo derivative VII in 10 ml ethanol by analogy to procedure B for the synthesis of XIa. The yield of XIb was 0.58 g (100%), mp 130°C.

REFERENCES

1. Yu. M. Yutilov and I. A. Svertilova, Khim. Geterotsikl. Soedin., No. 1, 97 (1986).
2. J. S. Wieczorek and T. Talik, Roczn. Chem., **36**, 967 (1962).
3. Yu. M. Yutilov and I. A. Svertilova, Khim. Geterotsikl. Soedin., No. 8, 1071 (1994).
4. K. S. Roos and C. A. Salemink, Rec. Trav. Chim., **88**, 1263 (1969).
5. C. A. Salemink and C. W. Wan der Want, Rec. Trav. Chim., **68**, 1013 (1949).
6. A. V. Stetsenko and N. S. Miroshnichenko, Ukr. Khim. Zh., **39**, 703 (1973).