AZAINDOLE DERIVATIVES

XXXIX.* REACTIONS OF 6-CHLORO-7-AZAINDOLINES WITH AMINES

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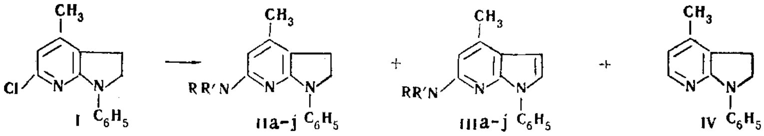
In addition to normal nucleophilic substitution, redox processes to form dehalogenation products of 7-azaindoline and the corresponding oxidized compounds – 6-amino-7-azaindole derivatives – occur during the reactions of various primary and secondary amines with 6-chloro-7-azaindolines. The quantitative ratios of the products of nucleophilic substitution and the redox reaction depend mainly on the nucleophilicity of the attacking amine and, by selecting the amine component of the reaction, one can accomplish either predominantly nucleophilic substitution or direct the process primarily along the path of the redox reaction.

The two-ring 7-azaindoline system is characterized by the presence of an electron-accepting nitrogen in the pyridine part of the molecule and a pyrroline nitrogen that, owing to the +M effect, reduces the electron deficit in the 4- and 6-positions. As a result, as was noted in [2], the halogen atom in 6-chloro-7-azaindolines undergoes substitution only at 190-250°C even under the action of such strong nucleophilic agents as the alkali metal alkoxides. Even more severe conditions are required for the reaction of 6-chloro-7-azaindolines with amines.

In a study of the reaction of 1-phenyl-4-methyl-6-chloro-7-azaindoline (I) with cyclic secondary amines we observed that, in addition to normal nucleophilic substitution, redox processes to form the dehalogenated compound, 1-phenyl-4-methyl-7-azaindoline (IV), and the corresponding oxidation products – 1-phenyl-4-methyl-6-amino-7-azaindole derivatives (III) – also occur [1].

Subsequent investigations showed that the ambiguous course of the reaction is general for the reaction of 6-chloro-7-azaindolines with various primary and secondary aliphatic, aliphatic-aromatic, and aromatic amines. Moreover, depending on the amine used, the chief reaction may be either normal nucleophilic substitution of the halogen atom or redox processes to form dehalogenated 7-azaindoline.

A polarographic investigation demonstrated that various 6-amino-7-azaindolines (IIa-i) can, with about the same ease ($E_{1/2}$ 0.29-0.43) and considerably more readily than the corresponding 6-chloro derivative of I ($E_{1/2}$ 0.91), be oxidized to 7-azaindoles with simultaneous reduction of I to 1-phenyl-4-methyl-7-azaindoline. Thus, $E_{1/2}$ of II is not the determining factor in the predominance of one or another direction



a $R=R'=-(CH_2)_4-$; b $R=R'=-(CH_2)_5-$; c $R=R'=O(CH_2CH_2)_2$; d $R=R'=CH_3N(CH_2CH_2)_2$;
e $R=R'=CH_3$; f $R=R'=C_4H_9$; g $R=C_4H_9, R'=H$; h $R=C_6H_5, R'=H$; i $R=C_6H_5, R'=C_2H_5$;
j $R=R'=C_6H_5CH_2$

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*See [1] for communication XXXVIII.

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for the reaction. The quantitative ratios of the products of nucleophilic substitution and the redox reaction depend mainly on the nucleophilicity of the attacking amine.

Moreover, in the case of cyclic secondary amines (pyrrolidine, piperidine, morpholine, and N-methylpiperazine), steric factors that hinder attack by the amine are virtually absent, and the deciding factor is the pK_a of the amine. Up to 90% of the normal product of nucleophilic substitution (II) and only about 1% each of the dehalogenated compound (IV) and substituted 7-azaindole (II) are formed with more basic amines (pyrrolidine and piperidine, pK_a 11.22-11.27). When a weaker base (morpholine, pK_a 8.39) is used, the overall yield of products of substitution of chlorine in I by an amine residue (II + III) decreases to 64%, while the amount of III and IV increases to 7-8% each. The reaction is shifted to favor IV to an even greater degree when N-methylpiperazine is used: the yield of 6-amino derivatives II and III is 56%, while the amount of dehalogenation product IV increases to 28%.

In the case of primary and secondary aliphatic amines (dimethylamine, butylamine, and dibutylamine), in addition to the pK_a of the attacking amine, steric hindrance arising during the interaction of the amine with I also begins to have an effect. Only this can explain the fact that although dibutylamine (pK_a 11.25) is a stronger base than dimethylamine (pK_a 10.73), the overall yield of 6-dimethylamino derivatives IIe and IIIe is 48.5%, approaching the yields in similar reactions with sterically unhindered cyclic amines, while the yield of 6-dibutylamino derivatives IIf and IIIf does not exceed 26%. In addition, on passing from dimethylamine to dibutylamine, the specific weight of the second path of the reaction – the redox process – increases markedly, and the yield of IV increases from 0.6 to 25%. Since steric hindrance in the reaction of I with butylamine occupies an intermediate position as compared with the analogous reactions of the two secondary aliphatic amines considered above, while the basicity of butylamine is somewhat lower (pK_a 10.66), in this case one observes a further decrease in the overall yield of products of the nucleophilic substitution of chlorine by an amine residue (IIg + IIIg) to 15%, while the amount of IV formed occupies an intermediate position as compared with the yields of IV in analogous reactions of I with dibutyl- and dimethylamines. Thus, a decrease in the basicity of the amine and an increase in the steric hindrance during its attack – two factors which reduce the nucleophilicity of the amine – inhibit the normal nucleophilic substitution of halogen in I by an amine residue and promote reduction of chloro derivative I to IV through oxidation of the 6-aminoazaindolines (II) to substituted 6-aminoazaindoles (III).

This tendency is manifested to an even greater extent for dibenzylamine, in which the relatively low pK_a (8.30) and considerable steric hindrance direct the process primarily to favor the redox reaction. This direction is also facilitated by the high reduction potential of dibenzylamine, through the oxidation of which IV is formed in 16% yield, while the overall yield of the products of normal nucleophilic substitution of chlorine by an amine residue (IIj + IIIj) is 0.6%. It should be noted that on passing from sterically unhindered cyclic amines to aliphatic primary and secondary amines and to dibenzylamine, the amount of 6-chloroazaindoline (I) that does not react increases sharply from 0.5-0.9 to 44-64%.

Despite their low basicities (pK_a 4.60-5.12), aromatic amines (aniline and N-ethylaniline) do not react sufficiently completely with the starting chloroazaindoline (I). In addition to the above-noted nucleophilic substitution with the formation of II and the redox process leading to III and IV, other products arise in this reaction: under the reaction conditions, II and III undergo further transformations. This was demonstrated by special experiments with the addition of definite amounts of II and III to the starting compounds; the amounts of II and III changed during the reaction. The inadequate overall yields of identified reaction products (60-68%) also attest to processes associated with more profound changes in the compounds. Nevertheless, as in the other cases, the increase in the steric hindrance in aromatic amines on passing from aniline to N-ethylaniline resulted in a decrease in the overall yield of products of normal nucleophilic substitution (II and III) from 46.5 to 25%. The yield of the product of the redox reaction (IV) increased simultaneously. In the case of N-ethylaniline, IV was the major product and was obtained in 42% yield. It is interesting to note that in the reaction of I with N-ethylaniline, in addition to nucleophilic substitution, we also observed N-dealkylation; in addition to 1-phenyl-4-methyl-6-(N-phenyl-N-ethylamino)-7-azaindoline, 1-phenyl-4-methyl-6-phenylamino-7-azaindoline and 1-phenyl-4-methyl-6-phenylamino-7-azaindole were detected in the reaction products by gas-liquid chromatography. We have previously [3] noted similar N-dealkylation in the synthesis of 6-(N-aryl-N-alkylamino)-7-azaindolines.

EXPERIMENTAL

All of the investigations of the reaction of I with amines were carried out in a 180-ml steel autoclave by heating 6.12 g (25 mmole) of I with 50 mmole of the amine at 250° for 10 h. After alkalization, the reaction products were extracted with benzene and separated from resin by vacuum distillation, and a sample was collected for gas liquid chromatography (GLC). The remaining substance was subjected to preparative separation. A "Pai" argon chromatograph with β-ionization detection was used for the GLC. The 1.2 by 4 mm column was packed with E-301 silicone elastomer (3%) on silanized Cellite 545 (80-100 mesh). The column temperature was 230°, and the argon flow rate at the exit was 50 ml/min. The relative retention time was determined from I, for which the retention time was 5.4 min. The products of the reaction of I with dimethylamine were separated with a column of the above dimensions packed with polyethylene glycol adipate (2%) on silanized Cellite (80-100 mesh). The column temperature was 215°, and the argon flow rate was 60 ml/min at the outlet. The relative retention times of IIe and IIIe, which are presented in Tables 2 and 3, were determined from I, for which the retention time was 30 min under these conditions.

All of the results of GLC analysis are presented in Table 1.

The products of the reaction of I with N-methylpiperazine were fractionated for preparative separation. The fraction with bp 190-220° (1 mm) was recrystallized from alcohol to give 0.96 g (18%) of IV, which was identical to the substance described in [5] with respect to melting point and IR spectrum. After trituration with acetone, 2.78 g of IId was obtained from the fraction with bp 220-230° (1 mm).* The products of the reaction of I with morpholine were recrystallized from acetone to give 2.76 g of IIc. The mother liquor was evaporated, and the residue was vacuum distilled. After recrystallization from methanol, an additional 0.83 g of IIc was obtained from the fraction with bp 210-225° (1 mm). The fraction with bp 176-200° (1 mm) was dissolved in benzene, and the solution was washed with 6% hydrochloric acid. After alkalization and extraction with benzene, 0.35 g of IV was isolated from the aqueous acidic solution. After removal of the basic substances, evaporation, and crystallization of the residue from methanol, 0.37 g (6.1%) of I was obtained from the benzene solution. After recrystallization from alcohol, 6.38 g of IIa and 5.28 g of IIb, respectively, were isolated from the products of the reaction of I with pyrrolidine and piperidine. The products of the reaction of I with dimethylamine were dissolved in 17% hydrochloric acid, and 2.61 g (42.7%) of I was extracted with benzene. The aqueous acidic solution was made alkaline, and the base was extracted with benzene and recrystallized from ethyl acetate to give 1.57 g of IIe. The products of the reaction of I with butylamine were treated with 17% hydrochloric acid, and the unchanged I [3.5 g (57%)] was extracted with benzene. The mixture of IIg, IIIg, and IV obtained after alkalization of the hydrochloric acid solution was hydrogenated in alcohol with a Pd catalyst in order to convert IIIg to IIg. To separate IIg and IV, the mixture was dissolved in benzene, and IV was extracted with 6% hydrochloric acid. After crystallization

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* The properties, constants, and yields of the compounds obtained are presented in Table 2.

TABLE 1. Products of the Reaction of 1-Phenyl-4-methyl-6-chloro-7-azaindoline (I) with Amines

RR′NH			Yield, %				Overall yield of identified reaction products, %
R	R′	pK_a [4]	I	II	III	IV	
$-(CH_2)_4-$		11,27	0,53	91,8	0,85	0,62	93,8
$-(CH_2)_5-$		11,22	1,1	90,0	0,75	1,0	92,8
$O(CH_2CH_2)_2$		8,39	8,8	57,4	6,9	8,8	82,2
$CH_3N(CH_2CH_2)_2$		—	0,51	47,7	8,2	27,7	84,1
CH_3	CH_3	10,73	50,2	47,9	0,59	0,59	99,3
C_4H_9	C_4H_9	11,25	43,8	10,1	16,0	24,9	94,8
C_4H_9	H	10,66	57,3	8,85	6,39	14,3	86,8
$C_6H_5CH_2$	$C_6H_5CH_2$	8,3	63,5	—	—	16,4[c]	80,5
C_6H_5	H	4,60	—	22,0	24,5	13,3	59,8
C_6H_5	C_2H_5	5,12	0,56	20,1[b]	1,55 3,39[b]	42,3	67,9

[a] The yield was determined by GLC.

[b] $R = C_6H_5$, $R' = H$.

[c] After hydrogenation of the reaction mixture, 0.57% of 1-phenyl-4-methyl-6-amino-7-azaindoline was found.

TABLE 2. 6-Amino-Substituted 7-Azaindolines

Compound	Mp, °C	Rel. retention time	$E_{1/2}$, V	λ_{max}, nm (lg ε)	Empirical formula	Found, %			Calc., %			Yield, %
						C	H	N	C	H	N	
IIa	164—165[б]	3,64	0,32	—	$C_{18}H_{21}N_3$	77,7	7,3	15,1	77,4	7,6	15,0	91,5
IIb	119—120[б]	3,87	0,32	234 (4,13), 283 (4,29), 343 (4,30)	$C_{19}H_{23}N_3$	77,3	7,7	14,2	77,8	7,9	14,3	72,2
IIc	159—160[в]	4,10	0,40	232 (4,13), 283 (4,26), 342 (4,30)	$C_{18}H_{21}N_3O$	73,4	7,3	14,2	73,2	7,2	14,2	48,7
IId	132—133[в]	5,20	0,42	232 (4,33), 283 (4,45), 342 (4,49)	$C_{19}H_{24}N_4$	73,7	7,8	18,2	74,0	7,8	18,2	36,3
IIe	151—152[г]	0,61	0,32	232 (4,10), 282 (4,26), 345 (4,30)	$C_{16}H_{19}N_3$	76,2	7,7	16,3	75,9	7,6	16,6	40,5
IIf	81—82[б]	4,26	0,32	237 (4,09), 285 (4,27), 350 (4,32)	$C_{22}H_{31}N_3$	78,1	9,0	12,5	78,3	9,3	12,4	9,8
II g	76—77[б]	2,60	0,29	226 (4,07), 282 (4,22), 344 (4,30)	$C_{18}H_{23}N_3$	76,8	8,3	14,7	76,8	8,2	14,9	5,2
IIh	—	8,90	0,43	269 (4,24), 295 (4,36), 350 (4,30)	$C_{20}H_{15}N_3$	—	—	—	—	—	—	—
II i	104—105[б]	6,20	0,40	249 (4,12), 277 (4,31), 353 (4,40)	$C_{22}H_{21}N_3$	80,4	6,9	12,6	80,2	7,0	12,8	3,2[д]

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[a] The preparative yield is presented.

[b] From alcohol.

[c] From acetone.

[d] From ethyl acetate.

[e] After hydrogenation over Pd.

TABLE 3. 6-Amino-Substituted 7-Azaindoles

Compound	Bp, °C (press., mm)	Mp, °C	Relative retention time	λ_{max}, nm (lg ε)	Empirical formula	Found, %			Calc., %			Yield, %
						C	H	N	C	H	N	
IIIb	206—208 (2)	63—64[a]	2,57	256 (4,35), 295 (4,02), 324 (4,01)	$C_{19}H_{21}N_3$	78,3	7,1	14,7	78,3	7,3	14,4	41,4
IIIc	220—222 (2)	147—148[b]	2,63	257 (4,35), 294 (4,01), 318 (4,02)	$C_{18}H_9N_3O$	74,1	6,8	14,8	73,7	6,5	14,3	81,7
IIId	212—215 (2)	125—126[b]	3,46	257 (4,34), 294 (4,02), 318 (4,02)	$C_{19}H_{22}N_4$	74,8	7,4	18,3	74,5	7,2	18,3	53,7
IIIe	—	77—78[a]	0,51	241 (4,27), 258 (4,32), 295 (3,94), 327 (4,00)	$C_{16}H_{17}N_3$	76,3	6,9	16,9	76,5	6,8	16,7	87,3
IIIf	—	39—40[a]	2,88	257 (4,34), 300 (3,97), 331 (4,05)	$C_{22}H_{29}N_3$	78,9	8,7	12,4	78,7	8,7	12,5	67,1
III g	195—196 (0,3)	—	1,67	240 (4,27), 256 (4,30), 320 (4,95)	$C_{18}H_{21}N_3$	77,5	7,4	14,7	77,4	7,6	15,0	67,2
IIIh	228—230 (2)	110—111[c]	5,73	257 (3,78), 333 (4,32)	$C_{20}H_{17}N_3$	80,6	5,8	14,0	80,2	5,7	14,0	80,5
IIIi	233—234 (3)	—	3,90	259 (3,83), 332 (4,33)	$C_{22}H_{23}N_3$	81,0	6,8	13,0	80,7	7,0	12,8	73,2

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[a] From alcohol.

[b] From acetone.

[c] From methanol.

from alcohol, 0.37 g (5.2%) of IIg was obtained from the benzene solution, while 0.47 g (8.9%) of IV was obtained from the hydrochloric acid solution after removal of the base, extraction with benzene, and recrystallization from methanol. Similar workup of the products of the reaction of I with dibutylamine gave 2.18 g (35.7%) of I, 1.24 g (23.6%) of IV, and 0.83 g (9.8%) of IIf. The multi-component mixture formed after reaction of I with N-ethylaniline was not completely separated but was dissolved in benzene and extracted with 6% hydrochloric acid. After isolation and fractional distillation of the bases, 1.56 g (29.7%) of IV with bp 176-177° (2 mm) was obtained. The reaction of I with N-ethylaniline in an open vessel, which proceeds differently than in an autoclave and is not accompanied by N-dealkylation, was used for the preparative isolation of IIi. According to GLC, carrying out this reaction at 250° for 7 h leads to the formation of 93.6% I, 0.2% IIi, and 2.8% IV; at 300° (7 h) the reaction products contain 87.2% I, 1.2% IIi, 1.1% IIIi, and 1.0% IV; at 300° (30 h), the products contain 82.8% I, 4.5% IIi, 3.5% IIIi, and 0.8% IV. After heating for 30 h at 300°, the reaction mixture was made alkaline and extracted with benzene. The bulk of the starting I (4.24 g) was separated by crystallization from methanol. The remaining mixture was hydrogenated in the presence of a Pd catalyst and separated chromatographically with a column packed with Al_2O_3; 0.26 g (3.2%) of IIi was eluted with hexane–ether (1 : 1). In connection with the fact that the products of the reaction of I with dibenzylamine could not be preparatively separated, and IIj and IIIj for the reference spots necessary for GLC analysis were not available, the amounts of normal products of nucleophilic substitution were determined in an overall manner, after hydrogenation with a Pd catalyst, as 1-phenyl-4-methyl-6-amino-7-azaindoline [2]. For this, both GLC and anode polarography were used. The two methods gave comparable results.

Volt-ampere curves were recorded with a PA-101 polarograph (Yanagimoto, Japan). The $E_{1/2}$ values of 1-phenyl-4-methyl-6-amino-7-azaindoline and of all the other compounds were determined by polarographic oxidation on a platinum rotating disc N electrode (1880 rpm, $q = 0.031\ cm^2$). Ethanol with 0.5 N $NaClO_4$ was used as the indifferent electrode at 25 ± 0.05°. The comparison electrode was a saturated calomel half cell. The accuracy in the measurements of the half-wave potentials was ±0.01 V. The results are presented in Table 2. For 1-phenyl-4-methyl-6-amino-7-azaindoline, $E_{1/2} = 0.40$ V.

The independent synthesis of IIIb-i was accomplished by dehydrogenation of 1.5 g of IIb-i by refluxing for 1.5 h with an equal weight of chloranil in xylene. After cooling, the xylene solution was washed with 10% sodium hydroxide and water, dried, and vacuum evaporated. The residue was then distilled. The yields, constants, and analysis of the compounds obtained are presented in Table 3. The structures of IIIb-i were also confirmed by UV spectroscopy. The spectra of alcohol solutions, recorded with an EPS-3 spectrophotometer (Tables 2 and 3), show that the hypsochromic shift of the long-wave maxima that is typical for such transitions [3,5] is observed on passing from substituted 7-azaindolines IIb-i to the corresponding 7-azaindoles IIIb-i.

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