5,6-DIHYDRO-4H-IMIDAZOLE[4,5,1-i,j]QUINOLINE DERIVATIVES

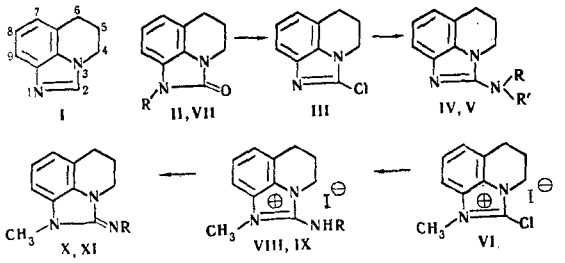
I. SYNTHESIS AND TRANSFORMATIONS OF 2-AMINO DERIVATIVES

V. G. Poludnenko and A. M. Simonov

UDC 547.781.5'831.3:543.422.6

2-Alkyl(dialkyl)amino derivatives of I and their respective cyclic ammonium salts were obtained by reaction of the 2-chloro derivative of 5,6-dihydro-4H-imidazole[4,5,1-i,j]quinoline (I) and its methiodide with amines. The cycloammonium salt was converted into 2-amino(alkylimino)-1,2-dihydro derivatives of I. Methoxy- and methyl-substituted I readily formed 2-amino derivatives by reaction with sodium amide. Comparison of the UV spectra of the 2-amino derivative of I and its fixed tautomeric form indicates that the 2-amino derivative of I exists primarily in the amino form in dioxane and CCl_4.

Compounds of the 5,6-dihydro-4H-imidazole[4,5,1-i,j]quinoline (I) series have been studied to only a relatively small extent. We have examined several paths for the synthesis and properties of 2-amino- and 2-alkyl(dialkyl)amino derivatives of this heterocycle (IV-V) as well as its 2-imino-1,2-dihydro derivatives (X-XI).



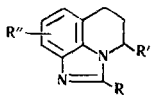
II R=H; VII R=CH_3; IV R=CH_3, R'=H; V R=R'=CH_3; X R=H; XI R=CH_3; VIII R=H; IX R=CH_3

The 2-chloro derivative (III) is formed in good yield by reaction of phosphorus oxychloride with 5,6-dihydro-4H-imidazolono[4,5,1-i,j]quinoline (II). The halogen atom in III can be readily replaced by alkyl and dialkylamino groups; however, the starting material (III) was recovered after reaction with ammonium hydroxide. Reaction with methyl iodide quantitatively converts 2-chloro-5,6-dihydro-4H-imidazo[4,5,1-i,j]-quinoline into methiodide VI, in which the chlorine atom is so labile that its replacement by amino and alkylamino groups to form VIII and IX commences at 20°. However, while the formation of 2-amino derivative VIII occurs by reaction of VI with ammonium hydroxide, replacement of the chlorine atom by a methylamino group and subsequent transformation to free imine XI is possible only in absolute alcohol in order to avoid hydrolysis to VII.

A convenient method for the introduction of an amino group in the 2 position of imidazole systems is direct Chichibabin amination. As we previously reported, 5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline (I) and its 8-methoxy derivative are readily converted to 2-amino derivatives by reaction with sodium amide [1]. Extending our study of this reaction, we subjected a number of other derivatives of I to amination and found that it proceeds successfully in all cases (Table 1).

Rostov-on-Don State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1410-1413, October, 1970. Original article submitted July 25, 1969.

TABLE 1. 5,6-Dihydro-4H-imidazo[4,5,1-i,j]quinoline Derivatives



R	R′	R″	mp (solvent)	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
H	H	7-CH_3O	127—128 (n-Octane)	$C_{11}H_{12}N_2O$	69,96	6,61	14,76	70,19	6,43	14,88	80[a]
H	CH_3	8-CH_3O	115—116 (n-Oxtane)	$C_{12}H_{14}N_2O$	71,41	6,71	13,79	71,26	6,98	13,85	86[a]
H	CH_3	8-CH_3	106—107 (n-Octane)	$C_{12}H_{14}N_2$	77,53	7,34	15,12	77,38	7,58	15,04	92[a]
NH_2	H	7-CH_3O	234—235 [b]	$C_{11}H_{13}N_3O$	65,10	6,57	20,52	65,00	6,45	20,67	75[a]
NH_2	CH_3	8-CH_3O	227—228 (aqueous alcohol)	$C_{12}H_{15}N_3O$	66,65	6,88	19,45	66,34	6,96	19,34	50[c]
NH_2	CH_3	8-CH_3	234—235 (water)	$C_{12}H_{15}N_3$	71,93	7,27	20,89	71,61	7,51	20,88	40[c]

a. The compound was obtained by heating the dihydrochloride of the 1,2,3,4-tetrahydroquinoline derivative with formic acid under reflux for 5 h.
b. Purified by sublimation.
c. A solution of 0.005 mole of imidazoquinoline in dimethylaniline was added dropwise to a suspension of 0.01 mole of sodium amide in dimethylaniline heated to 120°. The mixture was held at this temperature for 1.5 h, cooled, and 5 ml of water was added. The precipitate was filtered and washed with petroleum ether and water.
d. The amination was carried out at 150° under the same conditions as in c.

To obtain the starting compounds the methyl and methoxy derivatives of o-nitroanilines were converted to compounds of the quinaldine series according to the modified method in [2] (45% and 40% yields, respectively), which were then subjected to reduction according to the method in [3] to 1,2,3,4-tetrahydro derivatives. In order to decrease their oxidation, the latter were conveniently isolated and introduced into the cyclization with formic acid in the form of dihydrochlorides.

On the basis of a study of the IR spectra of 2-amino-5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline (XII) and its deuteration product, it was recently established that XII exists primarily in the amino form in chloroform [4] rather than the imino form as Richardson supposed [5]. This conclusion is also confirmed by comparison of the UV spectra of IV, XII, and the fixed tautomeric forms of these compounds – 2-dimethylamino derivative V and imines X and XI.

In dioxane the UV spectra of IV and XII are similar to the spectrum of V and differ from the spectra of imines X and XI. There are two absorption bands for these compounds in dioxane: in the spectra of the 2-amino-, 2-methylamino-, and 2-dimethylamino derivatives they lie, respectively, at 257 and 288, 257 and 291, and 260 and 291 nm, while for imines X and XI they are found at 265 and 304, and 275 and 315 nm (Fig. 1). A similar phenomenon occurs for the UV spectra in CCl_4, where one absorption band is observed: 291 nm in the spectra of IV and V, 286 nm for XII, 314 nm for X, and 306 nm for XI.

EXPERIMENTAL

5,6-Dihydro-4H-imidazolono[4,5,1-i,j]quinoline (II). A mixture of 11 g (0.05 mole) of 1,2,3,4-tetrahydro-8-aminoquinoline dihydrochloride and 6.0 g (0.1 mole) of urea was fused at 140° for 30 min. The product was purified by reprecipitation from 10% hydrochloric acid to give 8.4 g (97%) of II with mp 210° (210-211° [6]).

2-Chloro-5,6-dihydro-4H-imidazo[4,5-i,j]quinoline (III). A mixture of 1.0 g of II and 6 ml of phosphorus oxychloride was heated to 140°; after dissolution of all of the precipitate the solution was cooled to 110°, and HCl was passed through it for 3 h. The reaction mixture was cooled, and the excess $POCl_3$ was decomposed with ice. The solution was neutralized with cooling with 20% NaOH, and the resulting precipitate

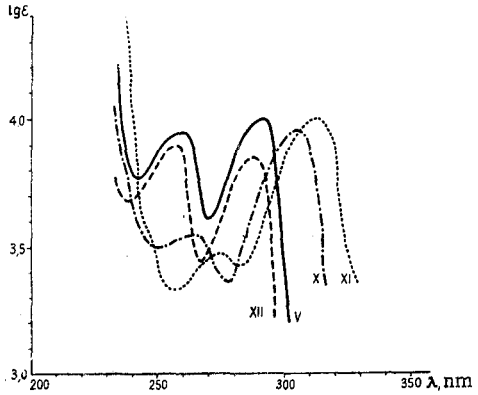


Fig. 1. UV spectra: V) 2-dimethylamino-5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline; X) 2-imino-1-methyl-5,6-dihydro-4H-imidazolino[4,5,1-i,j]quinoline; XI) 2-methylimino-1-methyl-5,6-dihydro-4H-imidazolino[4,5,1-i,j]quinoline; XII) 2-amino-5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline.

was filtered to give 0.90 g (82%) of colorless crystals with mp 75-76° (from water). Found %: N 14.48. $C_{10}H_9ClN_2$. Calculated %: N 14.55.

2-Methylamino-5,6-dihydro-4H-imidazo[4,5,1-i,j]-quinoline (IV). A mixture of 1.4 g of III and 4.5 ml of 25% aqueous methylamine was heated at 150° in an autoclave for 4 h. The mixture was cooled, and the precipitate was filtered to give 1.2 g (92.3%) of colorless prisms with mp 222-223° (from toluene). Found %: C 70.41; H 7.12; N 22.55. $C_{11}H_{13}N_3$. Calculated %: C 70.56; H 7.00; N 22.44.

2-Dimethylamino-5,6-dihydro-4H-imidazo[4,5,1-i,j]-quinoline (V). A mixture of 1.4 g of III, 1.62 g of dimethylamine hydrochloride, 5 ml of water, and 1.5 g of sodium carbonate was heated at 150° for 4 h. The reaction product was extracted with chloroform and chromatographed on aluminum oxide to give 1.32 g (93.7%) of an oil with bp 195-200° (20 mm). Found %: N 20.68. $C_{12}H_{15}N_3$. Calculated %: N 20.88. The pure substance absorbed water avidly to form a monohydrate in the form of colorless crystals with mp 63-64° (from water). Found %: C 65.98; H 7.90; N 18.98. $C_{12}H_{15}N_3 \cdot H_2O$. Calculated %: C 65.73; H 7.82; N 19.16.

2-Chloro-5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline Methiodide (VI). Compound III [0.90 g (0.005 mole)] was dissolved in 2 ml of absolute benzene, 2 ml (0.03 mole) of methyl iodide was added, and the mixture was heated on a water bath for 15 min. The precipitate which formed after several hours was filtered, washed with benzene, and subjected to further transformations. The yield was almost quantitative (1.7 g).

1-Methyl-5,6-dihydro-4H-imidazolono[4,5,1-i,j]quinoline (VII). A mixture of 1.67 g of VI and 10 ml of 25% aqueous methylamine was heated in a water bath for 3 h. The solution was evaporated, and the residue was recrystallized from water to give 0.52 g (55%) of colorless plates with mp 120-121°. Found %: C 69.98; H 6.68; N 14.80. $C_{11}H_{12}N_2O$. Calculated %: C 70.19; H 6.43; N 14.88.

2-Amino-5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline Methiodide (VIII). A mixture of 1.17 g of VI and 15 ml of 25% ammonium hydroxide was heated on a water bath for 3 h. The mixture was cooled, and the precipitate was filtered and recrystallized from water to give 0.90 g (60%) of colorless prisms that melted above 305°. Found %: N 13.16. $C_{11}H_{14}IN_3$. Calculated %: N 13.33.

2-Methylamino-5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline Methiodide (IX). A mixture of 1.67 g (0.005 mole) of VI and 1.55 g (0.05 mole) of methylamine in 6 ml of absolute methanol was refluxed for 3 h. The mixture was cooled, and the precipitate was filtered to give 1.10 g (60%) of colorless prisms with mp 284-285° (from water). Found %: N 12.60. $C_{12}H_{16}IN_3$. Calculated %: N 12.76.

2-Imino-1-methyl-5,6-dihydro-4H-imidazolino[4,5,1-i,j]quinoline (X). Compound VIII (0.50 g) was dissolved by heating in water and 10 ml of 10% NaOH was added. The oil which separated on cooling crystallized to give 0.25 g (83%) of colorless prisms with mp 91-92° (from benzene–petroleum ether). Found %: C 70.36; H 7.16; N 22.50. $C_{11}H_{13}N_3$. Calculated %: C 70.56; H 7.00; N 22.44.

2-Methylimino-1-methyl-5,6-dihydro-4H-imidazolino[4,5,1-i,j]quinoline (XI). Sodium [0.07 g (0.003 g-atom)] was dissolved in 5 ml of absolute ethanol, and 0.65 g (0.003 mole) of IX was added to the solution in small portions. After dissolution of the precipitate the alcohol was removed by distillation, and the residue was recrystallized from petroleum ether to give 0.35 g (61%) of colorless prisms with mp 93-95°. Found %: C 71.32; H 7.55; N 20.97. $C_{12}H_{15}N_3$. Calculated %: C 71.61; H 7.51; N 20.88.

5-Methoxy-8-aminoquinoline (XIII). Stannous chloride [54 g (0.24 mole)] was dissolved in 80 ml of water and 40 ml of concentrated hydrochloric acid. The solution was cooled with ice water, and a solution of 15 g (0.075 mole) of 5-methoxy-8-nitroquinoline in 100 ml of concentrated hydrochloric acid was added dropwise. The mixture was stirred for 30 min, after which it was heated on a water bath for 1 h. The mixture was cooled, made strongly alkaline, and extracted with chloroform. The residue after removal of the

solvent was distilled in vacuo at 135° (7 mm) to give 6.6 g (50%) of pale-yellow plates with mp 90-91° (from aqueous alcohol). Found %: C 68.69; H 5.78; N 16.29. $C_{10}H_{10}N_2O$. Calculated %: C 68.95; H 5.79; N 16.08.

8-Amino-5-methoxy-1,2,3,4-tetrahydroquinoline (XIV). Sodium (10 g) was added in small portions with stirring to a refluxing solution of XIII in 80 ml of absolute ethanol. The reaction mixture was heated for 1.5 h, cooled, 100 ml of water was added, and the mixture was extracted with toluene. The extract was evaporated under nitrogen to one-third of its original volume, washed three times with water, and the diamine was extracted with hydrochloric acid (1 : 1). The acidic solution was evaporated to give 6.7 g (77%) of the dihydrochloride. The picrate was obtained in the form of pale-red prisms with mp 160° (from aqueous alcohol). Found %: C 47.42; H 4.51; N 17.16. $C_{16}H_{17}N_5O_8$. Calculated %: C 47.18; H 4.21; N 17.19.

2-Methyl-6-methoxy-8-nitroquinoline (XV). Acetaldehyde (160 g) was added to a mixture of 500 ml of concentrated HCl and 100 g of 3-nitro-4-aminoanisole cooled to −15°. The mixture was held at −10° for 1.5 h, 136 g of zinc chloride was added, and the temperature was slowly raised to 0° in 3 h. The mixture was then heated on a water bath at 60° for 4 h. The reaction mass was poured into 2 liters of water, boiled with charcoal, filtered, and neutralized. The precipitate was separated, dried, extracted with toluene, and the extract was treated with hydrochloric acid (1 : 1). The acidic solution was boiled with charcoal, filtered, cooled, and neutralized with NaOH to give 52 g (40%) of a product with mp 185-186° (from aqueous alcohol) (186° [7]).

2,6-Dimethyl-8-nitroquinoline (XVI). This was obtained in 45% yield in the form of yellowish-white prisms with mp 118-119° (from aqueous alcohol) from 3-nitro-4-aminotoluene in the same way as XV. Found %: C 65.46; H 4.77; N 14.04. $C_{11}H_{10}N_2O_2$. Calculated %: C 65.34; H 4.98; N 13.85.

2,6-Dimethyl-8-aminoquinoline (XVII). This was obtained in 70% yield in the form of yellow plates with mp 105-106° (from alcohol) from XVI in accordance with [8]. Found %: C 76.73; H 7.19; N 16.32. $C_{11}H_{12}N_2$. Calculated %: C 76.71; H 7.02; N 16.27.

8-Amino-2,6-dimethyl-1,2,3,4-tetrahydroquinoline (XVIII). The dihydrochloride was obtained in 94% yield from XVII in the same way used to obtain XIV. The dipicrate was obtained in the form of greenish-yellow plates with mp 163-165° (decomp., from alcohol). Found %: C 43.85; H 3.67; N 17.90. $C_{23}H_{22}N_8O_{14}$. Calculated %: C 43.54; H 3.50; N 17.66.

LITERATURE CITED

1. A. M. Simonov and V. G. Poludnenko, Khim. Geterotsikl. Soed., 567 (1969).
2. W. H. Mills, J. E. Harris, and H. Lambourne, J. Chem. Soc., 1294 (1922).
3. R. C. Elderfield and F. J. Kreysa, J. Am. Chem. Soc., 70, 44 (1948).
4. R. T. C. Brownlee, A. R. Katritsky, and R. D. Topson, J. Chem. 567 (1969).
5. A. Richardson, J. Org. Chem., 28, 2581 (1963).
6. A. Richardson and E. D. Amstutz, J. Org. Chem., 25, 1139 (1960).
7. R. H. Baker, C. J. Albisetti, R. M. Dodson, J. R. Lappin, and B. Riegel, J. Am. Chem. Soc., 68, 1532 (1946).
8. V. M. Dziomko and I. A. Krasavin, Khim. Geterotsikl. Soed., No. 1, 281 (1967).