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

III.* SUBSTITUTION REACTIONS IN THE 5,6-DIHYDRO-4H-IMIDAZO[4,5,1-i,j]QUINOLINE SERIES

A. M. Simonov and V. G. Poludnenko

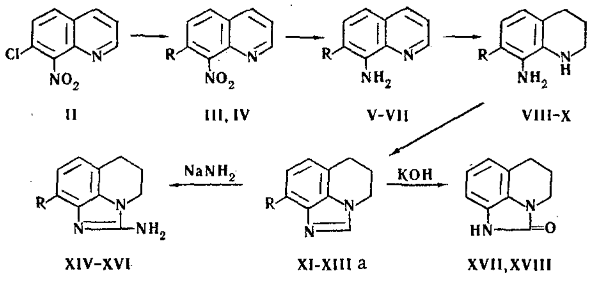
UDC 547.781.5'831.3

9-Substituted 5,6-dihydro-4H-imidazo[4,5,1-i,j]quinolines were synthesized and aminated by the action of sodium amide and hydroxylated by fusing with potassium hydroxide. The mononitro and dinitro compounds of some 5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline derivatives and the corresponding amino and diamino compounds were obtained. The latter react with nitric or formic acids to form a new heterocyclic ring.

To study the substitution reactions in the 5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline (I) series, we synthesized its 9-phenoxy- and 9-diethylamino derivatives (XI, XII) starting from 7-chloro-8-nitroquinoline (II) [2] (see the scheme below).

The reduction of the nitro group in III and IV with iron in dilute acetic acid leads to 8-amino derivatives V and VI. The action of sodium and alcohol on V, VI, and 7-methyl-8-aminoquinoline (VII) [3] converts them to 1,2,3,4-tetrahydro derivatives (VIII-X), which are subsequently converted to XI-XIIIa by heating with formic acid.

The ionization constants of the compounds obtained measured in 5% aqueous alcohol according to the method in [4], are 5.00 for XI, 6.90 for XII, and 6.03 for XIIIa; i.e., they lie in the range where the amination reaction is possible [4]. In fact, heating XI-XIIIa with sodium amide in dimethylaniline at 120°C gives their 2-amino derivatives (XIV-XVI).



III, V, VIII, XI, XIV $R=OC_6H_5$; IV, VI, IX, XII, XV, XVII $R=N(C_2H_5)_2$; VII, X, XIIIa XVI, XVIII $R=CH_3$

Like other imidazole-containing systems [7], XII and XIIIa could also be hydroxylated at the 2-position by fusing with potassium hydroxide at 280°C. Like 1-methylbenzimidazole [8], I and the 4,8-dimethyl and 7-methoxy derivatives of I [6] are smoothly converted to 2-mercapto derivatives (XIX-XXI) by fusing with sulfur.

---

* See [1] for communication II.

Rostov State University, Rostov-on-Don. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 242-246, February, 1972. Original article submitted January 25, 1971.

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

Compound	Mp, °C	Solvent	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
XI	110—112	Ether	$C_{16}H_{14}N_2O$	77,0	5,7	11,4	76,8	5,6	11,2	89
XII	88—89[a]	—	$C_{14}H_{19}N_3$	73,4	8,4	18,3	73,4	8,4	18,3	98
XIIIa	102—103	Octane	$C_{11}H_{12}N_2$	76,9	7,1	16,5	76,7	7,0	16,3	96
XIV	249—250	Butanol	$C_{16}H_{15}N_3O$	72,3	5,6	16,0	72,4	5,7	15,8	60
XV	124—125	Octane	$C_{14}H_{20}N_4$	68,5	8,0	22,9	68,8	8,2	22,9	45
XVI	258—259[b]	Water	$C_{11}H_{13}N_3$	70,3	6,7	22,3	70,6	7,0	22,4	70
XVII	153—154	Octane	$C_{14}H_{19}N_3O$	68,6	7,8	17,0	68,6	7,8	17,1	33
XVIII	213—214	Undecane	$C_{11}H_{12}N_2O$	70,5	6,5	14,9	70,2	6,4	14,9	58

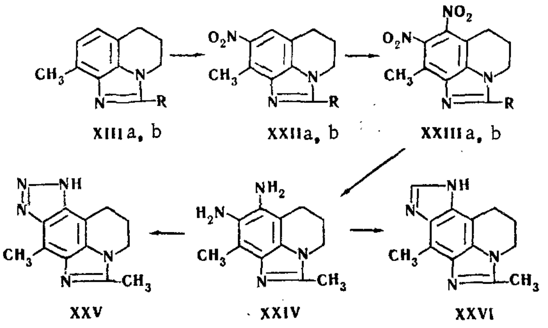
---

[a] Purified by sublimation.

[b] With decomposition.

The nitration of I in sulfuric acid with an equimolecular amount of 50% nitric acid at −15° leads (according to analysis) to the formation of a mixture of mononitro compounds in 81% yield. Thin-layer chromatography (TLC) on aluminum oxide in chloroform indicates the formation of three new substances with close R_f values. Apparently all three of the possible mononitro derivatives are formed.

Only one mononitro compound is obtained in 80 and 83% yield, respectively, by nitration of XIIIa and 2,9-dimethyl-5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline (XIIIb) [1] under similar conditions. It can be assumed that the nitro group enters the ortho position relative to the methyl group, i.e., the 8 position. Evidence in favor of this is the observation that XXIIa, b, like o- and p-nitrotoluenes [9], give an intense yellow coloration with dimethylaniline.



XXIIa XXIIIa R=H; XIIIb XXIIb XXIIIb $R=CH_3$

The reduction of XXIIb with stannous chloride leads to the 8-amino derivative of XIIIb (XXVII).

In order to ascertain the position of the nitro group in XXIIa, b by alternative synthesis, we attempted to obtain 7-amino-2,9-dimethyl-5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline. However, the hydrogenation of the starting 5,8-diamino-7-methylquinoline [10], according to [6], is accompanied by elimination of the 5-amino group, and subsequent heating of the resulting 1,2,3,4-tetrahydro derivative with acetic acid gives XIIIb.

A second nitro group enters into the ring of mononitro compounds XXIIa, b when they are treated with a mixture of 50% nitric acid and concentrated sulfuric acid at room temperature. To accelerate the reaction, the reaction mixture is heated on a water bath at 80° for 30 min. The yield is 70-80%. Reduction of XXIIIb with stannous chloride gave 7,8-diamino derivative XXIV in 90% yield. The action of nitric acid or heating with formic acid converts XXIV to new heterocyclic systems (XXV and XXVI).

EXPERIMENTAL

7-Phenoxy-8-nitroquinoline (III). A 62.4 g (0.3 mole) sample of 7-chloro-8-nitroquinoline was added in small portions with stirring to a melt of 120 g (1.27 mole) of phenol and 30 g (0.85 mole) of potassium hydroxide heated to 150°. The mixture was stirred for 1 h, cooled, and treated with 20% aqueous potassium hydroxide. The mixture was extracted with chloroform, and the chloroform extract was washed three times with 10% potassium hydroxide solution. The solvent was removed by distillation, and the residue was chromatographed on aluminum oxide in chloroform to give 56.1 g (71%) of greenish prisms with mp 84-85° (ethanol). Found: C 67.4; H 3.7; N 10.7%. $C_{15}H_{10}N_2O_3$. Calculated: C 67.7; H 3.8; N 10.5%.

7-Diethylamino-8-nitroquinoline (IV). A mixture of 20.8 g (0.1 mole) of 7-chloro-8-nitroquinoline, 20.8 ml (0.2 mole) of diethylamine, and 10 ml of alcohol was heated at 150° for 6 h. The reaction mass was then treated with 100 ml of water and extracted with chloroform. The chloroform extract was chromatographed on aluminum oxide to give 16.7 g (68%) of yellow prisms with mp 82-83° (octane). Found: C 63.7; H 6.0; N 17.3%. $C_{13}H_{15}N_3O_2$. Calculated: C 63.6; H 6.2; N 17.1%.

7-Phenoxy-8-aminoquinoline (V). A mixture of 30.0 g (0.11 mole) of III, 300 ml of water, and 6 ml (0.1 mole) of acetic acid was heated to the boiling point, and 34 g of iron filings was added in the course of 3 h with vigorous stirring. The mixture was then refluxed with stirring for 18 h and extracted with chloroform. The extract was dried with sodium sulfate, the solvent was removed by distillation, and the residue was vacuum distilled at 245° (7 mm) to give 18 g (70%) of greenish yellow plates with mp 73-74° (aqueous alcohol). Found: C 76.0; H 5.1; N 12.1%. $C_{15}H_{12}N_2O$. Calculated: C 76.3; H 5.1; N 11.9%.

7-Diethylamino-8-aminoquinoline (VI). This was similarly obtained from IV in 46% yield as an oil with bp 185° (18 mm). The picrate was obtained as yellow-green plates with mp 202-203° (dec., alcohol). Found: C 51.7; H 4.7; N 18.6%. $C_{13}H_{17}N_3 \cdot C_6H_3N_3O_7$. Calculated: C 51.4; H 4.5; N 18.9%.

7-Phenoxy, 7-Diethylamino, and 7-Methyl Derivatives of 8-Amino-1,2,3,4-tetrahydroquinoline (VIII-X). The dihydrochlorides were obtained from V-VII in 89, 95, and 94% yields, respectively, by the method in [6]. In view of the ready oxidizability of the compounds, they were introduced immediately into the cyclization reaction by the action of formic acid.

9-Phenoxy, 9-Diethylamino-, and 9-Methyl-5,6-dihydro-4H-imidazo[4,5,1-i,j]quinolines (XI-XIIIa). These compounds were obtained by refluxing the dihydrochlorides of VIII-X with formic acid for 5 h. The mixtures were neutralized with ammonia and extracted with chloroform, and the chloroform extract was chromatographed on aluminum oxide (see Table 1).

2-Amino Derivatives of XI-XIIIa (XIV-XVI). A mixture of 10 mmole of sodium amide and 5 mmole of XI in 5 ml of dimethylaniline was heated at 120° for 90 min, cooled, and poured into 5 ml of water. The resulting precipitate was removed by filtration and washed with ether and water. Compounds XII andXIIIa were similarly obtained (Table 1).

2-Oxo Derivatives (XVII, XVIII). A 1 g sample of 5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline derivative (XII, XIIIa) was fused with 5 g of anhydrous potassium hydroxide at 280° for 30 min. The melt was cooled, and 100 ml of water was added. The solid was removed by filtration and washed with water and 5% hydrochloric acid (Table 1).

8-Nitro-9-methyl-5,6-dihydro-4H-imidazo[4,5,1-i,j]quinolines (XXIIa). A 2.58 g (15 mmole) sample of XIIIa was dissolved in 10 ml of concentrated H_2SO_4, the solution was cooled to −15°, and a mixture of 1.4 ml (15 mmole) of HNO_3 (sp. gr. 1.32) and 3 ml of concentrated H_2SO_4 was added at a temperature no higher than −10°. The mixture was allowed to stand for 30 min and poured over 100 g of ice. The ice mixture was neutralized with ammonia and extracted with chloroform. The chloroform extract was chromatographed on aluminum oxide to give 2.5 g (80%) of pale-yellow prisms with mp 232-233° (butanol). Found: C 60.9; H 5.2; N 19.4%. $C_{11}H_{11}N_3O_2$. Calculated: C 60.8; H 5.1; N 19.3%.

7,8-Dinitro-9-methyl-5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline (XXIIIa). A 1 g (5 mmole) sample of XXIIa was dissolved at room temperature in 2 ml of concentrated H_2SO_4, 4 ml of HNO_3 (sp. gr. 1.32) was added, and the mixture was heated on a water bath at 80° for 30 min. It was then poured over 30 g of ice, and the ice mixture was neutralized with ammonia. The resulting precipitate was removed by filtration and washed with water to give 1.15 g (88.5%) of greenish plates with mp 202-204° (butanol). Found: C 50.1; H 3.7; N 21.4%. $C_{11}H_{10}N_4O_4$. Calculated: C 50.4; H 3.8; N 21.4%.

8-Nitro-2,9-dimethyl-5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline (XXIIb). This compound was similarly obtained from XIIIb [1] in 83% yield as light-yellow prisms with mp 164-165° (butanol). Found: C 62.1; H 5.6; N 18.2%. $C_{12}H_{13}N_3O_2$. Calculated C 62.3; H 5.7; N 18.2%.

8-Amino-2,9-dimethyl-5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline (XXVII). A 2.5 g (11 mmole) sample of XXIIb was introduced into a solution of 10 g (44 mmole) of $SnCl_2 \cdot 2H_2O$ in 40 ml of HCl (1 : 1), and the mixture was heated on a water bath for 2 h. It was then cooled and neutralized with 40% sodium hydroxide solution and extracted with chloroform. The chloroform extract was chromatographed on aluminum oxide, and the product was recrystallized to give 2.1 g (97%) of yellow prisms with mp 142-143° (water). Found: C 71.8; H 7.6; N 20.8%. $C_{12}H_{15}N_3$. Calculated: C 71.6; H 7.5; N 20.9%.

7,8-Dinitro-2,9-dimethyl-5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline (XXIIIb). This compound was similarly obtained from XXIIb in 67% yield as light-green prisms with mp 209-210° (butanol). Found: C 52.0; H 4.2; N 20.4%. $C_{12}H_{12}N_4O_4$. Calculated: C 52.2; H 4.4; N 20.3%.

7,8-Diamino-2,9-dimethyl-5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline (XXIV). A 4 g (14.5 mmole) sample of XXIIIb was introduced with stirring into a solution of 23 g (100 mmole) of $SnCl_2 \cdot 2H_2O$ in 40 ml of HCl (1 : 1), and the mixture was heated on a water bath for 2 h. It was then cooled and neutralized with 40% sodium hydroxide solution, and the diamine was extracted with chloroform. The extract was dried with potassium carbonate, and the solvent was removed by distillation to give 2.8 g (90%) of light-brown prisms with mp 151-152° (chloroform–ether). Found: C 66.3; H 7.3; N 25.9%. $C_{12}H_{16}N_4$. Calculated: C 66.6; H 7.5; N 25.9%.

4,5-Trimethylene-6,8-dimethylimidazo[4,5-*f*]benzotriazole (XXV). A solution of 2.6 g (12 mmole) of XXIV in a mixture of 4 ml of concentrated H_2SO_4 and 10 ml of water was poured into 60 g of ice. A solution of 1 g (14.5 mmole) of sodium nitrite in 3 ml of water was added with vigorous stirring in the course of 30 min, and the mixture was stirred until the ice dissolved, after which it was heated on a water bath for 3 h. It was then cooled and neutralized with ammonia, and the resulting precipitate was removed by filtration and washed with chloroform to give 1.4 g (51%) of light-gray tetrahedra with mp 355° (dec., dimethylformamide), pK_a (5% aqueous alcohol) 5.87. Found: C 63.4; H 6.1; N 31.1%. $C_{12}H_{13}N_5$. Calculated: C 63.4; H 5.8; N 30.8%.

3,4-Trimethylene-2,8-dimethylbenzo[1,2-d : 4,5-d'] diimidazole (XXVI). A mixture of 2 g (9.2 mmole) of XXIV, 10 ml of HCOOH, and 1 ml of concentrated HCl was refluxed for 5 h. Water (10 ml) was added, and the mixture was boiled with activated charcoal and filtered. The filtrate was cooled, neutralized with ammonia, and allowed to stand to precipitate 2.1 g (almost quantitative) of XXVI as colorless prisms with mp 300° (dec., water) and pK_a (5% aqueous alcohol) 6.88. Found: C 69.1; H 6.4; N 24.9%. $C_{13}H_{14}N_4$. Calculated: C 69.0; H 6.2; N 24.8%.

2-Mercapto-5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline (XIX). A 0.4 g (2.5 mmole) sample of I was triturated with 0.16 g (5 mg-atom) of sulfur, and the mixture was fused at 175° for 30 min. The melt was dissolved in 10% sodium hydroxide solution, and the solution was boiled with charcoal and filtered. The filtrate was neutralized with acetic acid, and the resulting precipitate was removed by filtration and washed with water to give 0.4 g (85%) of light-yellow prisms with mp 214-215° (aqueous alcohol) (mp 214-215° [11]).

2-Mercapto-4,8-dimethyl-5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline (XX). This compound was similarly obtained from 4,8-dimethyl-5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline [6] in 90% yield as yellowish prisms with mp 210-211° (octane). Found: N 12.7%. $C_{12}H_{14}N_2S$. Calculated: N 12.8%.

2-Mercapto-7-methoxy-5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline (XXI). This compound was similarly obtained from 7-methoxy-5,6-dihydro-4H-imidazo[4,5,1-i,j]quinoline [6] in 91% yield as yellowish prisms with mp 223-224° (butanol). Found: N 12.6%. $C_{11}H_{12}N_2OS$. Calculated: N 12.7%.

LITERATURE CITED

1. V. G. Poludnenko, A. M. Simonov, and L. G. Kogutnitskaya, Khim. Geterotsikl. Soedin., 967 (1971).
2. A. K. Sen, N. K. Ray, and U. P. Basu, J. Sci. Ind. Res., 11B, 325 (1952); Chem. Abstr., 47, 10,534e (1953).
3. R. Long and K. Schofield, J. Chem. Soc., 2350 (1953).
4. A. F. Pozharskii, A. M. Simonov, É. A. Zvezdina, and V. A. Anisimova, Khim. Geterotsikl. Soedin., 869 (1969).
5. A. M. Simonov and V. G. Poludnenko, Khim. Geterotsikl. Soedin., 567 (1969).
6. V. G. Poludnenko and A. M. Simonov, Khim. Geterotsikl. Soedin., 1410 (1970).
7. I. S. Kashparov and A. F. Pozharskii, Khim. Geterotsikl. Soedin., 124 (1971).
8. A. V. El'tsov and K. M. Krivozheiko, Zh. Organ. Khim., 2, 189 (1966).

9. Houben-Weyl, Methoden der Organ. Chem. [Russian translation], Vol. 2, Khimiya, Moscow (1967), p. 637.
10. R. Long and K. Schofield, J. Chem. Soc., 3161 (1953).
11. A. Richardson, J. Org. Chem., 28, 2581 (1963).