2-OXO-2,3-DIHYDROIMIDAZO[2,1-a]ISOQUINOLINE AND ITS TRANSFORMATIONS

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2-Oxo-2,3-dihydroimidazo[2,1-a]isoquinoline (I) was synthesized by the action of α-haloacetic acids on 1-aminoisoquinoline esters. The reactions of I with nitrous acid, acylating agents, aromatic aldehydes, p-nitrosodimethylaniline, and arenediazonium salts were studied. 3,3-Dihalo derivatives of this system with high reactivities of the halogen atoms were obtained.

Condensed systems obtained from 1-aminoisoquinoline display many-sided physiological activity [1-3]. This compelled us to undertake an investigation of the properties of the little-studied 2-oxo-2,3-dihydroimidazo-[2,1-a]isoquinoline (I) and its derivatives. This heterocyclic system was first obtained by splitting out of hydrogen halide from 1-chloroacetylaminoisoquinoline [4]. We have accomplished the synthesis of I by the action of α-haloacetic acid esters on 1-aminoisoquinoline. The intermediately formed imine cannot be isolated from the reaction mixture: Even in the cold, it immediately undergoes cyclization with the simultaneous formation of the hydrohalide of the starting amine. The presence in the PMR spectrum of 2-oxo derivative I of a singlet at δ 5.08 ppm, corresponding to the protons of the methylene group, and of a band of carbonyl absorption at 1680 cm^{-1} in its IR spectrum make it possible to assume that I exists primarily in the oxo form.

2-Oxo-2,3-dihydroimidazo[2,1-a]isoquinoline is resistant to hydrolysis and is converted to the hydrochloride by the action of hydrochloric acid, but, like the oxo derivatives of some other condensed imidazole systems with an active methylene fragment [5], it is readily oxidized in air to give deeply colored transformation products.

As expected, I reacts extremely readily with various electrophilic agents. Yellow isonitroso derivative II is liberated instantaneously when I is treated with sodium nitrite in dilute acetic acid solution. The isonitroso derivative is soluble in acids and alkalis, is very resistant to hydrolysis, and does not give complexes with divalent metal salts. Attempts to reduce it with zinc dust in acetic acid or with hydrazine hydrate on Raney nickel led to a complex mixture of substances.

Oxime II is smoothly acetylated when it is heated in acetic anhydride and gives a benzoyl derivative under the conditions of the Schotten–Baumann reaction. The band of stretching vibrations of an OH group observed in the spectrum of the starting oxime at 3430 cm^{-1} vanishes in the IR spectra of IIIa, b; the absorption band of the ring C=O group is shifted from 1700 to 1720-1725 cm^{-1}, and a band of high intensity that is characteristic for $\nu_{C=O}$ of an ester grouping appears at 1785-1790 cm^{-1}. On the basis of these data, acetoxy- and benzoxyimino derivative structures, respectively, were assigned to IIIa, b; this is in agreement with the recently published results of acylation of nitrosophenols [6].

In addition to 3-acetyl-substituted IV, the acylation of 2-oxoimidazoisoquinoline I with acetic anhydride gives 2-acetoxy-3-acetylimidazo[2,1-a]isoquinoline (V). The latter is extremely unstable and is converted to monoacetyl derivative IV on treatment with cold alkali or when it is heated in water. The structure adopted for diacetyl-substituted V was confirmed by the presence in its IR spectrum of two intense bands of carbonyl absorption at 1640 and 1760 cm^{-1} – acetyl and acetoxy groups, respectively.

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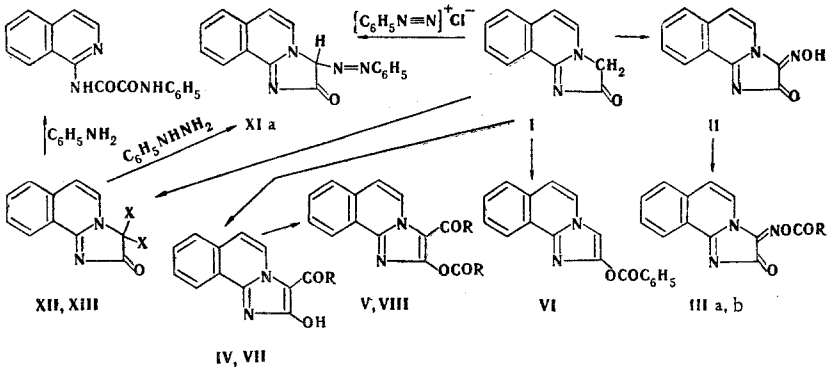
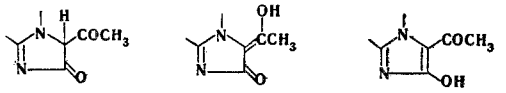


III a, IV, V R = CH_3; III b, VII, VIII R = C_6H_5; XII X = Br; XIII X = Cl

Three structures – ketone IVa and enols IVb and IVc – are possible for the monoacetyl-substituted compounds.



The absence in the PMR spectrum of IV (in trifluoroacetic acid)* of the signal of the H_3 proton makes is possible to exclude the possibility of the existence under these conditions of CH tautomer IVa (see [7]). The IR spectrum of a mineral oil suspension of the compound contains the absorption band of a C = O group at 1650 cm^{-1}; the band of stretching vibrations of the OH group does not appear, and this is probably due to the strong intramolecular hydrogen bond. Thus, on the basis of these data, it seems difficult to form a preference for one of the enol structures IVb or IVc.

The reaction of 2-oxoimidazoisoquinoline I with benzoyl chloride proceeds in different ways, depending on the reaction conditions. When the starting compounds are heated in pyridine, o-benzoyl derivative VI is primarily formed (in 87% yield), whereas benzoylation under the conditions of the Schotten–Baumann reaction proceeds at the carbon atom of the methylene group. Dibenzoyl derivative VIII was obtained by subsequent treatment of C-benzoyl-substituted VII with benzoyl chloride in pyridine. The IR spectra of VII and VIII are similar to the spectra obtained for acetyl-substituted IV and V. The carbonyl absorption band of the acetoxy group appears at 1730 cm^{-1} in the spectrum of O-benzoyl derivative VI.

2-Oxo-2,3-dihydroimidazo[2,1-a]isoquinoline condenses smoothly at the methylene group with aromatic aldehydes and p-nitrosodimethylaniline to give ylidene compounds (IXa-c) and corresponding imino derivative X. Coupling of X with arenediazonium chlorides yielded 3-arylazo derivatives of this system (XIa, b), which, in analogy with most compounds of the type under consideration, could have an arylhydrazone structure. However, there are no distinct bands of stretching vibrations of an NH bond in the IR spectra of XI, and the frequencies for the C = O bond (1670-1675 cm^{-1}) are of low intensity; in our opinion, this is due to the predominance of the azo form (see [8]).

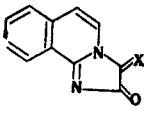
The high reactivities of the hydrogen atoms of the methylene group of 2-oxoimidazoisoquinoline are also manifested in halogenation. 3,3-Dihalo-substituted compounds are formed immediately in the case of an equimolar ratio of the starting reagents, and monohalogenation products cannot be isolated. 3,3-Dibromo-2-oxoimidazo[2,1-a]isoquinoline (XII) was obtained in good yield both by the action of N-bromosuccinimide (NBS) and by bromination with molecular bromine in acetic acid. In the latter case the reaction proceeds through an intermediate step involving the formation of the perbromide of dibromo derivative XII, which undergoes decomposition by sodium carbonate solution in the cold to give XII.

The synthesis of 3,3-dichloro derivative XIII was accomplished by treatment of I with 1-chlorobenzotriazole [9] (2 moles) in water. The fact that the compounds obtained are gem-dihalo derivatives was confirmed by their cleavage to 1-aminoisoquinoline as a result of acid hydrolysis.

The lability of the halogen atoms was studied in the case of dibromo-substituted XII. It was found that the latter is readily resinified by heating with solutions of alkalis and carbonates and highly basic amines. In addition, its reaction with aniline gives N-(1-isoquinolyl)-N'-phenyloxamide (XIV), the structure of which was proved by alternative synthesis by treatment of 1-butoxalylaminoisoquinoline with aniline.

*The spectrum of a solution in an aprotic solvent cannot be recorded because of the low solubility of IV.

TABLE 1. 2-Oxo-2,3-dihydroimidazo[2,1-a]isoquinoline Derivatives



Compound	X	mp, °C*	Empirical formula	Found, %			Calculated, %			Yield, %
				C	H	N	C	H	N	
II	NOH	237	$C_{11}H_7N_3O_2$	61,7	3,3	19,6	61,9	3,3	19,7	87
IIIa	$NOCOCH_3$	204	$C_{13}H_9N_3O_3$	61,4	3,7	16,2	61,2	3,5	16,5	92
IIIb	$NOCOC_6H_5$	225	$C_{18}H_{11}N_3O_3$	68,0	3,7	13,5	68,1	3,5	13,2	84
IXa	$CHC_6H_4NO_2$-*p*	298	$C_{18}H_{11}N_3O_3$	68,4	3,5	12,9	68,1	3,5	13,2	91
IXb	$CHC_6H_4N(CH_3)_2$-*p*	287	$C_{20}H_{17}N_3O$	76,3	5,2	13,1	76,1	5,4	13,3	87
IXc	$CHC_6H_3(OCH_3)_2$-3,4	242	$C_{20}H_{16}N_2O_3$	72,0	5,0	8,4	72,3	4,8	8,4	68
X	$NC_6H_4N(CH_3)_2$-*p*	257	$C_{19}H_{16}N_4O$	72,3	5,1	17,6	72,1	5,1	17,7	95

*Compounds II, IIb, IXa, and X were recrystallized from DMF, IIIa was recrystallized from acetic anhydride, and IXc was recrystallized from butanol.

Two compounds in approximately equal amounts were isolated by brief heating of dibromo derivative XII in an alcohol solution of phenylhydrazine. One of them is identical to the product of coupling of 2-oxoimidazo-isoquinoline with benzenediazonium chloride (XIa). The second was obtained as bright-red crystals with the same elementary composition as that of azo derivative XIa. However, its IR spectrum contains a distinct band of stretching vibrations of an NH group at 3300 cm^{-1} and a high-intensity band of a C=O group at 1730 cm^{-1}. It is therefore completely likely that this compound is 2,3-dioxoimidazo[2,1-a]isoquinoline 2-phenylhydrazone, but this should be confirmed by further study.

EXPERIMENTAL

The PMR spectra of trifluoroacetic acid solutions of the compounds were recorded with a Tesla BS 467 spectrometer (60 MHz, hexamethyldisiloxane as the internal standard). The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer.

2-Oxo-2,3-dihydroimidazo[2,1-a]isoquinoline (I). A solution of 4.32 g (0.03 mole) of 1-aminoisoquinoline and 2.2 g (0.015 mole) of methyl bromoacetate in 20 ml of alcohol was refluxed for 2 h, after which it was cooled, and the resulting precipitate was removed by filtration, washed with ether, and suspended in 10 ml of alcohol. A stream of dry ammonia was bubbled through the solution, during which colorless crystals precipitated from the initially formed dark-violet solution; after the odor of ammonia had vanished, these crystals were removed by filtration and washed with alcohol and acetone to give 2.3 g (74%, based on the converted amine) of slightly pinkish plates with mp 199-200° (from butanol). Found: C 71.9; H 4.5; N 15.0%. $C_{11}H_8N_2O$. Calculated: C 71.7; H 4.4; N 15.2%. The product was only slightly soluble in most organic solvents but dissolved readily in water. The hydrochloride had mp 265° (from water).

3-Hydroxyimino-2-oxoimidazo[2,1-a]isoquinoline (II). Two to three drops of glacial acetic acid and 0.14 g (2 mmole) of dry sodium nitrite were added to a solution of 0.27 g (1.5 mmole) of I in 5 ml of water, and the precipitate that formed after 15-20 min was removed by filtration and washed with water to give yellow needles that were only slightly soluble in chloroform and alcohol but quite soluble in acetone. See Table 1 forphysical characteristics.

3-Acetoxyimino-2-oxoimidazo[2,1-a]isoquinoline (IIIa). This compound was obtained as orange needles by heating hydroxyimino derivative II in acetic anhydride for 5-7 min (see Table 1).

3-Benzoxyimino-2-oxoimidazo[2,1-a]isoquinoline (IIIb). A solution of 0.21 g (1 mmole) of II in 3 ml of 3% sodium hydroxide solution was shaken with 0.14 ml (1.2 mmole) of benzoyl chloride, during which a bright-red precipitate formed instaneously (see Table 1).

Acylation of 2-Oxo-2,3-dihydroimidazo[2,1-a]isoquinoline. A solution of 0.54 g (3 mmole) of I in 5 ml of acetic anhydride was heated for 1 h. The resulting precipitate was a mixture of di- (V) and monoacetyl (IV) derivatives of the starting compound. The precipitate was removed by filtration and washed with ether and (repeatedly) with chloroform. The yield of monoacetyl-substituted IV, which was obtained as colorless prisms with mp > 300° [from dimethylformamide (DMF)], was 0.32 g (47%). Found: C 69.1; H 4.4; N 12.0%. $C_{13}H_{10}N_2O_2$. Calculated: C 69.0; H 4.4; N 12.0%. The product was only slightly soluble in most organic solvents and water but was soluble in dilute solutions of alkalis. The 2,4-dinitrophenylhydrazone was obtained as dark-brown crystals with mp > 300°. Found: N 20.4%. $C_{19}H_{14}N_6O_5$. Calculated: N 20.7%.

The mother liquor remaining after separation of IV was treated with ice water and neutralized with sodium charbonate, and the resulting precipitate was filtered to give 0.30 g (37%) of shiny colorless needles of

diacetyl derivative V with mp 164° (from alcohol). The product was soluble in chloroform and acetone but insoluble in water. Found: C 67.3; H 4.8; N 10.2%. $C_{15}H_{12}N_2O_3$. Calculated: C 67.2; H 4.5; N 10.4%.

2-Benzoxyimidazo[2,1-a]isoquinoline (VI). A mixture of 0.37 g (2 mmole) of 2-oxo derivative I and 0.25 ml (2 mmole) of benzoyl chloride in 5 ml of pyridine was refluxed for 15-20 min, after which the solvent was removed by distillation under reduced pressure, and the residue was treated with water. The solid material was removed by filtration and purified by chromatography with a column filled with Al_2O_3 (elution with chloroform) to give 0.51 g (87%) of colorless crystals with mp 158° (from ethyl acetate). Found: C 74.8; H 4.0; N 10.0%. $C_{18}H_{12}N_2O_2$. Calculated: C 75.0; H 4.2; N 9.7%. The product was isoluble in chloroform, acetone, and alcohol but insoluble in water.

3-Benzoyl-2-oxo-2,3-dihydroimidazo[2,1-a]isoquinoline (VII). A suspension of 0.37 g (2 mmole) of I in 3 ml of 5% sodium hydroxide solution was stirred and treated with 0.28 ml (2.5 mmole) of benzoyl chloride. After 2 h, the mixture was diluted to twice its original volume with water, and the resulting precipitate was removed by filtration to give 0.48 g (82%) of colorless needles with mp 286° (DMF). Found: C 75.2; H 4.3; N 10.1%. $C_{18}H_{12}N_2O_2$. Calculated: C 75.0; H 4.2; N 9.7%.

3-Benzoyl-2-benzoxyimidazo[2,1-a]isoquinoline (VIII). A solution of 0.57 g (2 mmole) of monbenzoyl derivative VII and 0.25 ml (2 mmole) of benzoyl chloride in 5 ml of pyridine was heated for 30 min, and the reaction product was isolated as described in the preparation of VI to give 0.62 g (79%) of colorless shiny prisms with mp 166° (from alcohol). Found: C 76.4; H 4.2; N 7.4%. $C_{25}H_{16}N_2O_3$. Calculated: C 76.5; H 4.1; N 7.1%.

3-Arylidene-2-oxo-2,3-dihydroimidazo[2,1-a]isoquinolines (IXa-c, Table 1). These compounds were obtained by heating equimolar amounts of I and the appropriate aldehydes in glacial acetic acid for 10-30 min. The precipitates were removed by filtration and washed with ether. The acetic acid salt of condensation prodcut IXb was formed with p-dimethylaminobenzaldehyde, and the solution was therefore diluted with water and neutralized with concentrated NH_4OH. Compounds IXa-c were only slightly soluble in most organic solvents and in water.

3-(p-Dimethylaminophenylimino)-2-oxoimidazo[2,1-a]isoquinoline (X). A 0.15-g (1 mmole) sample of p-nitrosodimethylaniline was added in the cold to a solution of 0.18 g (1 mmole) of 2-oxo derivative I in 5 ml of water, and a dark-violet precipitate began to form immediately. After 30 min, it was removed by filtration and washed with water and alcohol. The physical characteristics of X are presented in Table 1. IR spectrum, cm^{-1}: $\nu_{C=O}$ 1690 and $\nu_{C=N}$ 1630.

3-Phenylazo-2-oxo-2,3-dihydroimidazo[2,1-a]isoquinoline (XIa). A solution of a diazonium salt obtained from 0.09 ml (1 mmole) of aniline was added to a solution of 0.18 g (1 mmole) of I in 4 ml of glacial acetic acid containing 0.4 g of sodium acetate. After 1 h, the precipitate was removed by filtration and washed with water to give 0.23 g (79%) of orange needles with mp 262° (from CH_3COOH). Found: C 70.4; H 4.3; N 19.7%. $C_{17}H_{12}N_4O$. Calculated: C 70.8; H 4.2; N 19.5%.

3-(o-Nitrophenylazo)-2-oxo,2,3-dihydroimidazo[2,1-a]isoquinoline (XIb). This compound was similarly obtained. Workup gave bright-red shiny needles with mp 292° (DMF) in 85% yield. Found: C 61.4; H 3.6; N 21.2%. $C_{17}H_{11}N_5O_3$. Calculated: C 61.3; H 3.3; N 21.0%.

3,3-Dibromo-2-oxoimidazo[2,1-a]isoquinoline (XII). A) A solution of 0.85 ml (16 mmole) of bromine in 5 ml of acetic acid was added with stirring in the course of 25 min to a refluxing solution of 0.74 g (4 mmole) of I in 10 ml of acetic acid, after which the mixture was stirred for another 30 min. It was then cooled, and the brick-red precipitate of the perbromide of dibromo derivative XII was removed by filtration, washed with ether, and dried. The solid material (1.96 g) was treated in the cold with 20 ml of a saturated sodium bicarbonate solution, and the resulting yellow solid was removed by filtration and washed repeatedly with water to give 1.1 g (80%) of shiny yellow needles with mp 212° (dec., from CH_3COOH). Found: C 39.0; H 1.6; Br 46.5; N 8.0%. $C_{11}H_6Br_2N_2O$. Calculated: C 38.7; H 1.6; Br 46.7; N 8.2%. The product was soluble in chloroform but insoluble in water, alcohol, and benzene. IR spectrum, cm^{-1}: $\nu_{C=O}$ 1700.

B) A 0.37-g (2 mmole) sample of I was dissolved in 4 ml of acetic acid, and 0.72 g (4 mmole) of N-bromosuccinimide (NBS) was added in the cold with stirring. A yellow precipitate formed immediately; after 20 min, it was removed by filtration and washed with ether and a small amount of chloroform to give 0.46 g (67%) of XII. According to the results of chromatographic analysis and the melting points, the product was analogous to the compound obtained in method A.

3,3-Dichloro-2-oxoimidazo[2,1-a]isoquinoline (XIII). A 0.31-g (2 mmole) sample of 1-chlorobenzotriazole was added to a solution of 0.18 g of 2-oxo derivative I in 4 ml of water, and the mixture was stirred for 20 min.

The resulting precipitate was removed by filtration and washed with water and a small amount of alcohol and benzene to give 0.21 (83%) of lemon-yellow needles with mp 221° (dec., from alcohol). Found: C 52.0; H 2.4; Cl 27.7; N 11.0%. $C_{11}H_6Cl_2N_2O$. Calculated: C 52.1; H 2.4; Cl 28.0; N 11.1%. IR spectrum, cm^{-1}: $\nu_{C=O}$ 1740.

Reaction of 3,3-Dibromo-2-oxoimidazo[2,1-a]isoquinoline with Hydrochloric Acid. A pale-yellow precipitate of the extremely unstable hydrochloride of the starting compound was formed instantaneously when 0.68 g of dibromo derivative XII was heated in 5 ml of dilute (1 : 1) hydrochloric acid. After heating for 2 h, the solution was cooled, neutralized with sodium carbonate, and extracted with chloroform. Evaporation of the solvent gave 0.21 g (70%) of colorless crystals. No melting-point depression was observed for a mixture of this product with an authentic sample of 1-aminoisoquinoline.

1-Butoxalylaminoisoquinoline. A solution of 1.44 g (0.01 mole) of 1-aminoisoquinoline and 4 ml (0.02 mole) of dibutyl oxalate in 10 ml of alcohol was heated for 4 h, after which it was cooled, and the resulting precipitate was removed by filtration and washed with ether. Evaporation of the mother liquor yielded an additional amount of product for a total of 2.64 g (close to quantitative yield) of colorless prisms with mp 154-155° (from alcohol). Found: C 66.0; H 6.2; N 10.4%. $C_{15}H_{16}N_2O_3$. Calculated: C 66.2; H 5.9; N 10.3%. The product was readily soluble in water and chloroform.

N-(1-Isoquinolyl)-N'-phenyloxamide (XIV). A) A mixture of 0.34 g (1 mmole) of dibromo derivative XII and 0.37 ml (4 mmole) of aniline in 5 ml of alcohol was heated for 1 h, after which it was cooled, and the resulting precipitate was removed by filtration and washed with water to give 0.11 g (39%) of shiny colorless plates with mp 246° (from butanol). Found: C 69.8; H 4.6; N 14.0%. $C_{17}H_{13}N_3O_2$. Calculated: C 70.1; H 4.5; N 14.4%. IR spectrum, cm^{-1}: $\nu_{C=O}$ 1670 and ν_{N-H} 3320.

B) A solution of 0.27 g of 1-butoxalylaminoisoquinoline in 2 ml of aniline was refluxed for 1 h, after which it was cooled, and the resulting colorless precipitate was removed by filtration and washed with ether to give 0.23 g (79%) of XIV. The identical character of this product and the product obtained in method A was determined from the absence of a melting-point depression for a mixture of the substances and from their IR spectra.

Reaction of 3,3-Dibromo-2-oxoimidazo[2,1-a]isoquinoline with Phenylhydrazine. A mixture of 0.58 g (4 mmole) of phenylhydrazine hydrochloride and 0.33 g (4 mmole) of anhydrous sodium acetate in 10 ml of alcohol was heated for 3-5 min, after which 0.34 g (2 mmole) of dibromo derivative XII was added. The mixture was then refluxed for 1 h, and the precipitated inorganic salts were removed by filtration and washed with alcohol. The mother liquor was evaporated to dryness, and the residue was dissolved in 2 ml of chloroform and chromatographed with a column filled with Al_2O_3 (elution with chloroform). The first fraction contained 0.09 g of red needles, with mp 218° (from alcohol), the structure which was not established. The second fraction [0.12 g (41%)] was 3-phenylazo-2-oxo-2,3-dihydroimidazo[2,1-a]isoquinoline. It was identified by comparison of its IR spectrum with the spectrum of an authentic sample and by the absence of a melting-point depression for a mixture of the substances.

LITERATURE CITED

1. H. F. Hodson and A. W. Randall, British Patent No. 1356937 (1974).
2. D. E. Rodway and R. F. Cookson, British Patent No. 1347493 (1974).
3. P. K. Marshall, D. L. Pain, and K. R. Wooldridge, British Patent No. 1367146 (1974); Ref. Zh. Khim., 21, 0196P (1975).
4. B. R. Harriman, US Patent No. 2421693 (1947); Chem. Abstr., 41, 6830d (1974).
5. A. F. McKay and M. E. Kreling, Can. J. Chem., 40, 205 (1962).
6. E. Yu. Belyaev, T. N. Timofeeva, L. P. Semina, and L. M. Gornostaev, Zh. Org. Khim., 10, 1721 (1974).
7. A. Maquestiau, Y. Van Haverbeke, and R. N. Muller, J. Heterocycl. Chem., 12, 85 (1975).
8. M. O. Lozinskii, A. F. Shivanyuk, and P. S. Pel'kis, No. 7, 930 (1971).
9. C. W. Rees, and R. C. Storr, J. Chem. Soc., C, 1474 (1969).