ACID–BASE PROPERTIES OF 2,3,4,5-TETRAHYDRO-1H-NAPHTHO[2,3-b]-1,4-DIAZEPINE-2,4,6,11-TETRAONE

V. A. Loskutov, S. M. Lukonina,
A. V. Konstantinova, and E. P. Fokin

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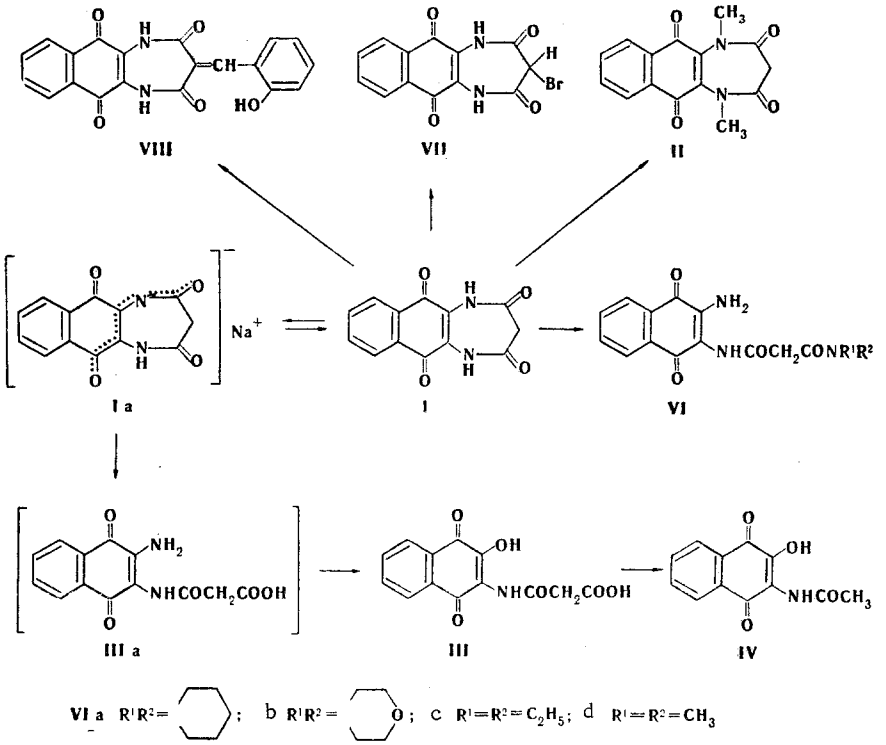
It is shown that 2,3,4,5-tetrahydro-1H-naphtho[2,3-b]-1,4-diazepine-2,4,6,11-tetraone, which has acid properties, undergoes methylation to give an N,N'-dimethyl derivative, whereas it gives products of substitution of the hydrogen atoms of the methylene group in its reactions with bromine and salicylaldehyde. Treatment of 2,3,4,5-tetrahydro-1H-naphtho[2,3-b]-1,4-diazepine-2,4,6,11-tetrone with aqueous alkali or secondary aliphatic amines with heating is accompanied by opening of the diazepine ring to give hydrolysis (2-carboxyacetamido-3-hydroxy-1,4-naphthoquinones) or aminolysis (N-alkylaminomalonyl-2,3-diamino-1,4-naphthoquinones) products.

We have previously [1] described the preparation of naphthodiazepinetetraone I. 1,5-Diazepine derivatives in which the 1,5-diazepine ring is condensed with a naphthoquinone (or anthraquinone) ring constitute a little-studied class of heterocyclic compounds, the benzo analogs of which have displayed high pharmacological activity [2]. In the present research we have examined the acid–base properties of naphthodiazepinetetraone I that determine its reactivity.

Compound I is stable with respect to the action of mineral acids (concentrated HCl) but undergoes hydrolysis of 2,3-diaminonaphthoquinone in concentrated sulfuric acid. In alkaline media diazepinetetraone I behaves like a relatively strong acid and forms colored solutions of salts.



Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Academy of Sciences of the USSR, Novosibirsk 630090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1132-1136, August, 1978. Original article submitted August 2, 1977.

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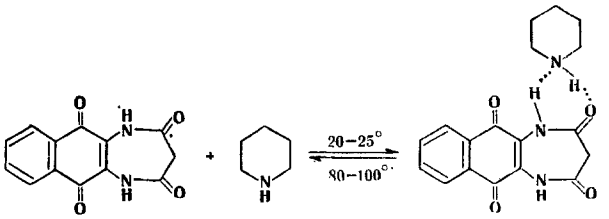
Compound I has two types of labile hydrogen atoms — amide and methylene. According to the data in [3], acetamido- and benzamidomalonic esters react with bases to give carbanions rather than N-anions. The UV spectrum of I in alkaline solution differs from the spectrum of I in ethanol with respect to a substantial bathochromic shift of the long-wave absorption maximum ($\Delta\lambda \sim 104$ nm); this constitutes evidence for the formation of an anion due to detachment of a proton from the nitrogen atom. The detachment of a proton from the carbon atom would have been accompanied by less significant changes in the UV spectrum. Thus the absorption maximum of 2,3,4,5-tetrahydro-1H-3-butylnaphtho[2,3-b]-1,4-diazepine-2,4,6,11-tetraone (418 nm in alcohol) in alkaline media is also shifted considerable ($\Delta\lambda$ 118 nm), while the analogous shift for N,N'-dimethyl derivative II, in the case of which only ionization of the C—H bond is possible, is 36 nm. The factor that is responsible for the high NH acidity of naphthodiazepinetetraone derivatives is undoubtedly the high electron-acceptor character of the naphthoquinone ring and the possibility of stabilization of anion Ia due to conjugation.

The acid—base interaction with the participation of I and bases depends on the pH of the medium and the temperature. Compound I, the long-wave absorption band of which in dimethyl sulfoxide (DMSO) lies at 410-420 nm, successively takes on red, red-violet, blue (changing to red-violet), and a persistent blue coloration as aqueous KOH solution is added gradually. The changes in the electronic absorption spectrum in the visible region that occur in this case are described as follows. During the initial addition of the alkali the electronic spectrum contains two maxima (410-420 and 520 nm) that attest to partial ionization. As the addition of alkali is continued, the first of the indicated maxima vanishes, and the intensity of the second maximum increases substantially; this evidently is in agreement with the existence of purely anionic form Ia. As compared with the IR spectrum of the starting acid, the IR spectrum (in perfluorinated kerosene) of the monosodium salt of I is characterized by the appearance of absorption bands at 1690 cm^{-1} and 1500-1600 cm^{-1} and by a decrease in the intensities of the bands corresponding to the amide fragment. During the subsequent addition of alkali the absorption maximum in the electronic spectrum is shifted bathochromically to 600 nm, and this evidently corresponds to the formation of a dianion.

The addition of very small amounts of a secondary aliphatic amine (for example, piperidine) to a solution of I in polar solvents (pyridine, DMSO, and alcohol) is also accompanied by the development of a red coloration, which changes to yellow when the solution is heated to 80-100°C; the original (red) color of the solution is restored when the solution is subsequently cooled to room temperature. The observed phenomenon of thermochromism is evidently due to the fact that the acid—base reaction in this case is not associated with detachment of a proton but rather is restricted to the formation of a hydrogen bond with the base; this hydrogen bond is cleaved as the temperature is raised. Structure Ib is extremely likely for the described interaction, since I dissolves to give a yellow solution in triethylamine (which is more basic than pyridine) or in pyridine without the addition of a secondary amine.



I Ib

A distinctive feature of alkaline solutions of I is their instability even at room temperature. Thus, in the presence of 5% aqueous KOH solution the color of the reaction mixture changes rather rapidly from red-violet to dark-red. Acidification gives a yellow precipitate of III, which is quite soluble in water. The presence of absorption at 3590 cm^{-1} (O—H) and 1730 cm^{-1} (C=O in carboxylic acids) is observed in the IR spectrum of the product (as compared with the starting compound). After sublimation (at 200°C), III is converted to orange product IV, the IR spectrum of which does not contain absorption bands of a carboxyl group; in addition to the signals of naphthoquinone protons (7.64 and 8.02 ppm), the singlet of a methyl group (2.28 ppm) and the signals of NH and OH protons (8.39 and 12.72 ppm) are visible in the PMR spectrum of IV. On the basis of these data, we assigned 2-carboxyacetamido-3-hydroxynaphthoquinone (III) and 2-acetamido-3-hydroxynaphtho-

TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C	Found, %			Empirical formula	Calc., %			PMR spectrum (d_6-DMSO), δ, ppm	Yield, %
		C	H	N		C	H	N		
II	264—267[a]	63,5	4,8	10,2	$C_{15}H_{12}N_2O_4$	63,4	4,2	9,9		50—60
III	186—188 and 215—223[b]	56,6	3,2	5,0	$C_{13}H_{19}NO_6$	56,7	3,3	5,1		67
IV	223—225[b]	61,9	3,8	6,1	$C_{12}H_9NO_4$	62,3	3,9	6,1		30
VIa	191—192,5[c] 207—208,5[a]	63,0	5,4	12,3	$C_{18}H_{19}N_3O_4$	63,6	5,6	12,3	9,26 (1H, NH), 7,6—8,0 (naphthoquinone ring 4H), 6,86 (2H, NH_2), 3,46 (6H, α-CH_2 and CH_2—C=O), 1,50 (6H, β,γ-CH_2)	79
VIb	238—240[c] 248—250[a]	59,2	4,8	12,1	$C_{17}H_{17}N_3O_5$	59,5	5,0	12,3	9,26 (1H, NH), 7,5—8,0 (naphthoquinone ring 4H), 6,83 (2H, NH_2), 3,46 (10H, CH_2)	31
VIc	172—174[c] 174—176[a]	62,0	5,6	12,5	$C_{17}H_{19}N_3O_4$	62,0	5,8	12,8	9,46 (1H, NH), 7,6—8,1 (naphthoquinone ring 4H), 6,93 (2H, NH_2), 3,33 (6H, CH_2), 1,06 (6H, CH_3)	16
VId	193—195[c] 200—202[a]	59,7	4,7	13,9	$C_{15}H_{15}N_3O_4$	59,8	5,0	13,9	9,36 (2H, NH), 7,7—8,1 (naphthoquinone ring 4H), 6,96 (2H, NH_2), 3,50 (2H, CH_2), 3,00 (3H, CH_3), 2,86 (3H, CH_3)	17
VII	259—263[a]			8,2[d]	$C_{13}H_7N_2BrO_4$			8,4		79
VIII	280—283[c]	66,2	3,2	8,0	$C_{20}H_{12}N_2O_5$	66,7	3,3	7,8		98

[a]From methanol. [b]From chloroform—petroleum ether. [c]From benzene. [d]In the analysis for C and Br we were unable to obtain convergent results.

quinone (IV) structures to the yellow and orange substances. It may be assumed that the reaction scheme includes a step involving hydrolytic opening of the diazepine ring with the intermediate formation of amino carobxylic acid IIIa, which subsequently undergoes conversion to hydroxy carboxylic acid III; the latter undergoes decarboxylation when it is heated. The replacement of an amino group by a hydroxyl group is well known in the literature [4]. Such mild reaction conditions — dilute alkali at 20-25°C — are unusual. This is probably a characteristic property of N-acetyl-2,3-diaminonaphthoquinone (V) and its derivatives. By means of a special experiment we established that the amino group in V is also readily hydrolyzed by reaction with aqueous alkali to give hydroxy derivative IV and 1H-2-methylnaphthimidazole-4,9-dione, which is, however, the principal product when the reaction is carried out in alcohol [5].

When I is heated in the presence of nitrogen-containing bases (piperidine, morpholine, diethylamine, and dimethylamine), it undergoes aminolysis accompanied by ring opening. It was established that amides VI are formed as a result of the reaction. The characteristics of the products are presented in Table 1. The constants of amide VIa obtained as a result of reaction of diazepinetetraone I with piperidine were in complete agreement with the constants of the corresponding compound synthesized by reaction of N-ethoxymalonyl-2,3-diaminonaphthoquinone with piperidine. The spectral data for the amides are in agreement with the assigned structure, and their ability to develop polymorphic forms that differ with respect to their IR spectra, the color of their crystals, and their melting points are in agreement with the properties of N-ethoxymalonyl derivatives of 2,3-diaminonaphthoquinone [1].

Being a relatively strong NH acid, I is readily alkylated by diazomethane or methyl iodide (in alkaline media) to give N,N'-dimethyl derivative II. The IR spectrum of product II does not contain absorption bands at 3000-3600 cm^{-1}; in addition to a multiplet of naphthoquinone protons (7.94 ppm), the PMR spectrum of II contains two singlets (3.17 and 3.30 ppm) with an intensity ratio of 3:1 that correspond to methyl and methylene groups.

Although they are less acidic than the amide hydrogen atom, the hydrogen atoms of the methylene group of I have high reactivities with respect to electrophilic substitution.

3-Bromo derivative VII (probably containing a disubstituted product) is formed by the action of bromine on diazepinetetraone I in acetic acid. In addition to signals of four aromatic protons, the PMR spectrum of VII contains signals of two NH groups (10.46 ppm), which vanish on deuteration, and of a CH group (5.46 ppm). o-Hydroxybenzylidene derivative VIII was obtained by reaction of I with salicylaldehyde in pyridine. In addition to the absorption at 3270 and 3290 cm^{-1} that is characteristic for cyclic amides, the IR spectrum of the product contains a band at 3448 cm^{-1}, which corresponds to the absorption of the O–H group. Unfortunately, its low solubility did not make it possible to investigate the spectrum of VIII in organic solvents.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with Perkin–Elmer-180 and UR-20 spectrometers. The UV spectra of solutions of the compounds in alcohol and 0.1 N alcoholic KOH* were recorded with a Specord UV-vis spectrometer. The PMR spectra of 3-5% solutions of the compounds in $(CD_3)_2SO$ or $CDCl_3$ were obtained with a Varian A-56/56A spectrometer (60 MHz) with tetramethylsilane as the internal standard (the chemical shifts on the δ scale are presented). Silica gel was used for chromatography (elution with chloroform).

2,3,4,5-Tetrahydro-1H-naphtho[2,3-b]-1,4-diazepine-2,4,6,11-tetraone Sodium Salt (Ia). A solution of sodium ethoxide (from ∿0.05 g of sodium and 3 ml of ethanol) was added to a warm (∿50°C) solution of 0.23 g (0.7 mmole) of N-ethoxymalonyl-2,3-diaminonaphthoquinone [1] in 12 ml of ethanol, after which the mixture was filtered, and the filtrate was allowed to stand in a refrigerator for 24 h. The resulting dark-red crystals were separated, washed with alcohol, and dried to give 0.11 g (50%) of product. Found: C 56.2; H 2.8; N 10.1; incombustible residue 8.4%. $C_{13}H_7N_2O_4Na$. Calculated: C 56.1; H 2.5; N 10.1; Na 8.3%.

Aminolysis of N-(Piperidinomalonyl)-2,3-diamino-1,4-naphthoquinone (VIa, see Table 1). A) A mixture of 0.5 g (1.9 mmole) of diazepinetetraone I, 2 ml (20 mmole) of piperidine, and 50 ml of pyridine was refluxed for 7 h until the solid dissolved completely. The solvent was then removed by vacuum distillation to one-fourth of the original volume, and the residue was poured into water. The aqueous mixture was acidified and extracted with chloroform, and the extract was chromatographed to give 0.53 g of VIa.

Compounds VIc-d were similarly obtained.

B) A mixture of 0.1 g (0.3 mmole) of N-ethoxymalonyl-2,3-diaminonaphthoquinone, 1 ml (10 mmole) of piperidine, and 5 ml of pyridine was refluxed for 2.5 h, after which it was worked up as in the preceding experiment to give 0.04 g (38%) of a product with mp 190-191°C (from benzene).

Hydrolysis. 2-Carboxyacetamido-3-hydroxy-1,4-naphthoquinone (III) and 2-Acetamido-3-hydroxy-1,4-naphthoquinone (IV). A) A mixture of 0.2 g (0.76 mmole) of diazepinetetraone I and 5 ml of 5% KOH was maintained at 20-25°C for 17 h (or refluxed for 1-2 min), after which it was acidified with 4 N HCl, and the yellow precipitate (0.19 g) was removed by filtration and divided into two equal portions. One portion was recrystallized from chloroform–petroleum ether to give 0.07 g of yellow crystals of III. The second portion of the precipitate was subjected to vacuum sublimation (at ∿1 mm) at 200°C to give 0.03 g of orange crystals of IV.

B) A mixture of 0.2 g (0.09 mmole) of N-acetyl-2,3-diamino-1,4-naphthoquinone (V) and 5 ml of 5% KOH solution was refluxed for 1-2 min, after which it was acidified with 4 N HCl, and the precipitate was removed by filtration and washed with water until the wash waters were almost colorless. This procedure gave 0.02 g (11%) of yellow crystals of 1H-2 methylnaphth[2,3-d]imidazole-4,9-dione with mp 360-365°C (dec.) (mp 368°C [5]). The aqueous filtrate was acidified and extracted with chloroform, and petroleum ether was added to the extract to precipitate 0.06 g (30%) of IV, which was identical to a sample of the compound obtained by method A. The product had mp 222-224°C (mp 219-220°C [6]).

2,3,4,5-Tetrahydro-1H-3-n-butylnaphtho[2,3-b]-1,4-diazepine-2,4,6,11-tetraone. A 2-ml sample of 5% KOH solution was added to a solution of 0.1 g (0.3 mmole) of N-(2-ethoxycarbonylheptanoyl)-2,3-diamino-1,4-naphthoquinone [1] in 60 ml of methanol, and the mixture was

*The UV spectra of I in DMSO at various pH values were recorded by V. N. Kobrina.

maintained at 20-25°C for 24 h. It was then acidified, and the orange precipitate was separated and chromatographed to give 0.09 g (42%) of a product with mp 251-252.5°C (from benzene). IR spectrum (cm^{-1}): 1630 sh, 1655, and 1715 (C=O); 3120, 3200, and 3260 sh (N–H). Found: C 65.9; H 5.2; N 9.0%. $C_{19}H_{20}N_2O_4$. Calculated: C 65.4; H 5.1; N 9.0%.

2,3,4,5-Tetrahydro-1H-1,5-dimethylnaphtho[2,3-b]-1,4-diazepine-2,4,6,11-tetraone (II). A) An excess amount of an ether solution of diazomethane was added to a solution of 0.12 g (0.5 mmole) of diazepinetetraone I in a mixture of 50 ml of DMSO and 50 ml of diethyl ether, and the mixture was maintained at 5-10°C for 2 days, after which it was poured into water. The aqueous mixture was extracted with chloroform, the chloroform was removed from the extract by evaporation, and the residue was chromatographed to give 0.07 g of II.

B) A mixture of 0.25 g (1 mmole) of diazepinetetraone I, 0.35 g (0.25 mmole) of potassium carbonate, and 30 ml of DMSO was stirred at 20-25°C until the color changed from yellow to red-violet (20-30 min). Methyl iodide [1 ml (16 mmole)] was added, and the mixture was stirred for 30 min, after which it was worked up as in the preceding experiment to give 0.16 g of II.

2,3,4,5-Tetrahydro-1H-3-bromonaphtho[2,3-b]-1,4-diazepine-2,4,6,11-tetraone (VII). A mixture of 0.2 g (0.8 mmole) of diazepinetetraone I, 0.08 ml (1.6 mmole) of bromine, and 20 ml of glacial acetic acid was refluxed for 10-15 min until the solid dissolved completely. The solution was then poured into water, and the aqueous mixture was extracted with chloroform. The product was recrystallized from methanol to give 0.26 g of VII.

2,3,4,5-Tetrahydro-1H-o-hydroxybenzylidenenaphtho[2,3-b]-1,4-diazepine-2,4,6,11-tetraone (VIII). A solution of 0.12 g (0.5 mmole) of diazepinetetraone I, 0.5 ml (5 mmole) of piperidine, and 50 ml of pyridine was maintained at 20-25°C for 1 h, after which it was poured into water, and the red precipitate was removed by filtration.

The characteristics of II-IV, VII, and VIII are presented in Table 1.

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