2,5-DIHYDRO-1H-4-METHYLNAPHTHO[2,3-b]-1,4-DIAZEPINE-2,6,11-TRIONE. REACTION WITH METHANOL

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UDC 547.655.6+547.892

The reaction of 2,3-diamino-1,4-naphthoquinone with acetoacetic ester in toluene (with water separation) gave 2,5-dihydro-1H-4-methylnaphtho[2,3-b]-1,4-diazepine-2,6,11-trione, which adds a molecule of methanol to the C=C bond of the diazepine ring to give 2,3,4,5-tetrahydro-1H-4-methyl-4-methoxynaphtho-[2,3-b]-1,4-diazepine-2,6,11-trione.

It is expedient to increase the number of subjects for investigation in order to solve the problem of the peculiarities of the tautomeric transformations of dihydronaphtho- and dihydroanthra-1,4-diazepinediones [1]. The preparation of 2,3-dihydro-1H-4-methylnaphtho-[2,3-b]-1,4-diazepinetrione (III) in the reaction of 2,3-diamino-1,4-naphthoquinone (I) with diketene and subsequent cyclization of the resulting acetoacetamido derivative (II) has been described. However, the possibility of tautomerism of the naphthodiazepinetrione, the benzo analog of which has isolated in the imine and enamine forms by recrystallization from various solvents [3], was not taken into account in [2].

We have established that the naphthodiazepinetrione does not have imine structure III but rather is an enamine (IV). Its UV spectra in organic solvents [alcohol, chloroform, and dimethyl sulfoxide (DMSO)] and in KBr are identical, and this excludes the possibility of tautomerism as a function of the aggregate state of the compound. Signals of a vinyl proton (4.48 ppm) and two NH groups (7.09 and 7.44 ppm), which constitute unambiguous evidence for the enamine structure of the compound, are visible in the PMR spectrum of the compound in d_6-DMSO, in addition to the singlet of protons of a methyl group (1.94 ppm) and a multiplet of naphthoquinone protons (7.87 ppm). We obtained II and IV, the melting points and IR spectra of which are in agreement with the published data [2], by a method that is widely used for the synthesis of dihydrobenzo(and pyrido)diazepinones [4], viz., by heating (with water separation) of diamine I and acetoacetic ester in toluene. The ratio of reaction products II and IV is determined by the reaction time: II was obtained in 63% yield after refluxing for 7 h, both II and IV are formed in a ratio of ~1:1 after 10-15 h, and the principal product is enamine IV (66%) after 20-30 h. The reaction of diamine I with acetoacetic ester was previously carried out [2] in methanol in the presence of acetic acid, but we were unable to obtain the dihydronaphthodiazepinetrione by this method.

On the basis of the data in [1, 3], one might have attempted to accomplish the conversion of the enamine form to the imine form by recrystallization from alcohol. With this end in mind, we treated enamine IV with methanol and isolated a dark-red substance. It was found that the conversion proceeds considerably more rapidly in the presence of catalytic amounts of acetic acid. The results of elementary analysis and the determination of the molecular weight of the compound were in agreement with a dihydronaphthodiazepinetrione structure containing one molecule of methanol; attempts to remove the methanol by heating (70-80°C) in vacuo did not lead to the desired result. We were able to split out a molecule of methanol by heating the compound to ~100°C in organic solvents (DMSO, acetic acid) or without a solvent but at a higher temperature (~200°C). As a result of this treatment the product of the addition of methanol was converted to starting enamine IV. The mass spectrum of the resulting dark-red substance contains a molecular ion peak ($M^{+\cdot}$) with m/e 286 (which coincides with the value calculated for $C_{15}H_{14}N_2O_4$) and an $M^+ - 32$ peak (loss of a molecule of methanol); the subsequent character of the fragmentation under the influence of electron impact is similar to that observed for enamine IV. Thus, in contrast to the benzo analog, treat-

Novosibirsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk 630090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 121-123, January, 1979. Original article submitted February 27, 1978.

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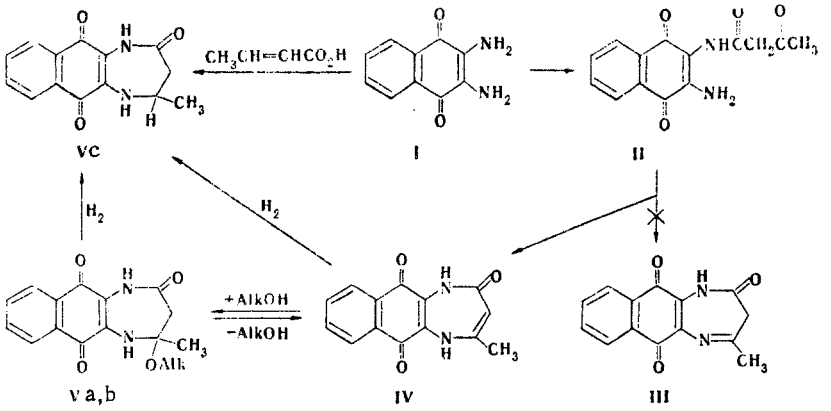

ment of dihydronaphthodiazepinetrione IV with methanol does not give imine form III but rather a chemical compound, to which we assigned tetrahydro derivative structure Va on the basis of the spectral data. Its IR spectrum differs from the spectrum of IV with respect to the more resolved structure of the bands in the region of the C=O stretching vibrations; the high-frequency region contains two bands (3280 and 3365 cm^{-1}) that correspond to vibrations of the N-H bonds. A multiplet (7.48-8.04 ppm) of naphthoquinone protons and two broad signals of NH protons (6.26 and 8.20 ppm), which vanish when the compound is deuterated, are visible in the PMR spectrum of Va (in $CDCl_3$). The signals of the protons of the methyl and methoxy groups are singlets at 1.64 and 3.16 ppm. The protons of the methylene group are observed in the form of a quartet (AB system, J_{AB} 15 Hz, δ_A 2.71 and δ_B 3.10 ppm); this confirms the structure of diazepine Va.

The addition of the less nucleophilic ethanol to enamine IV proceeds with greater difficulty: Vb was obtained in 10% yield after refluxing with ethanol for 20 h.

Alcohols evidently add to the C=C bond of the diazepine ring of enamine IV as in the case of the known [5] addition of nucleophiles to enamino ketones. The possibility of addition to the carbonyl group of the enamino ketone is excluded on the basis of the similarity in the IR (in the region of C=O and N-H stretching vibrations) and UV spectra of Va,b and tetrahydro derivative Vc, obtained by reaction of diamine I with crotonic acid. Another possible mechanism for the formation of Va,b as a result of the addition of a molecule of alcohol to the C=N bond (see [6]) of the tautomeric imine form of dihydronaphthodiazepinetrione III evidently is not realized, since dihydro-2,2,4-trimethylnaphthodiazepine-6,11-dione [1], which exists in the imine form in alcohol, remains unchanged when it is refluxed for a long time in methanol.

The same product — tetrahydro derivative Vc — the characteristics of which are in complete agreement with the characteristics of the product of the reaction of diamine I with crotonic acid, is formed in almost quantitative yield in the catalytic hydrogenation of IV and Va.

The peculiarities of the transformations of alcohol solutions of dihydrobenzo- and dihydronaphthodiazepinones can be explained by the different stabilities of the enamine forms, which should be increased for the naphthoquinone derivative due to hydrogen bonding between the NH group and the quinone carbonyl group (see [1]).

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a Perkin—Elmer 180 spectrometer. The PMR spectra of the compounds were recorded with Varian HA-100 (100 MHz) and Bruker AG WP-80 (80 MHz) spectrometers with tetramethylsilane as the internal standard (the chemical shifts are presented on the δ scale). The molecular weights of IV and Va and the elementary compositions of the ions were determined with an MS 902 spectrometer (with a direct-inlet system) at 120°C. Silica gel and chloroform were used for the chromatographic studies.

N-Acetoacetyl-2,3-diamino-1,4-naphthoquinone (II) and 2,5-Dihydro-1H-4-methylnaphtho-[2,3-b]-1,4-diazepine-2,6,11-trione (IV). A mixture of 1 g (5.3 mmole) of diamine I, 7 ml (54 mmole) of acetoacetic ester, and 75 ml of toluene was refluxed with a Dean—Stark adapter for 10-15 h, after which it was cooled, and the precipitate was removed by filtration,

washed with ether, and refluxed with 20-30 ml of methanol. The hot mixture was filtered, and the filtrate was allowed to stand, as a result of which 0.4 g (27%) of orange needles of II, with mp 187-189°C (mp 185-187°C [2]), precipitated. PMR spectrum (in d_6-DMSO): 9.30 (1H, unresolved signal, NH), 7.60-8.13 (4H, m, naphthoquinone protons), 6.76 (2H, m, NH_2), 3.60 (2H, s, CH_2), and 2.23 ppm (3H, s, CH_3).

The methanol-insoluble material was dissolved in chloroform and chromatographed to give 0.3 g (22%) of enamine IV with mp 248-251°C (mp 246-247°C [1]). Found: C 66.5; H 3.9; N 10.9%. M 254. $C_{14}H_{10}N_2O_3$. Calculated: C 66.1; H 3.9; N 11.0%; M 254.

2,3,4,5-Tetrahydro-1H-4-methyl-4-methoxynaphtho[2,3-b]-1,4-diazepine-2,6,11-trione (Va). A 0.13-g (0.5 mmole) sample of enamine IV was refluxed in 50 ml of methanol for 15 h, after which the mixture was evaporated to dryness, and the residue was dissolved in chloroform and chromatographed to give 0.1 g (71%) of a product with mp 250-252°C (from methanol). Found: C 63.2; H 4.7; N 9.7%; M 286. $C_{15}H_{14}N_2O_4$. Calculated: C 62.9; H 4.9; N 9.8%; M 286.

Ethoxy derivative Vb, with mp 247-249°C (from ethanol), was similarly obtained. Found: C 64.2; H 5.2; N 9.2%. $C_{16}H_{16}N_2O_4$. Calculated: C 64.0; H 5.3; N 9.3%.

2,3,4,5-Tetrahydro-1H-4-methylnaphtho[2,3-b]-1,4-diazepine-2,6,11-trione (Vc). A) A mixture of 0.2 g (1 mmole) of diamine I and 1 g (1.16 mmole) of crotonic acid was heated on a bath heated to 200°C for 20 min, after which it was cooled and dissolved in 20-30 ml of alcohol. The alcohol solution was poured into water, and the resulting precipitate was separated to give 0.26 g (96%) of a product with mp 208-210°C (from chloroform–methanol). IR spectrum: 1620, 1650, and 1670 (C=O); 3260 and 3300 cm^{-1} (N-H). PMR spectrum (in $CDCl_3$): 7.43-8.06 (5H, m, 4H from naphthoquinone and NH), 6.0 (1H, unresolved signal, NH), 3.86 (1H, m, CH), 2.76 (2H, m, CH_2), and 1.40 ppm (3H, d, J = 7 Hz, CH_3). Found: C 65.6; H 4.8; N 10.9%. $C_{14}H_{12}N_2O_3$. Calculated: C 65.6; H 4.7; N 10.9%.

B) A solution of 0.5 mmole of Va or Vb in 30 ml of absolute alcohol was hydrogenated over platinum dioxide. After the calculated amount of hydrogen had been absorbed, the catalyst was removed by filtration, and the solvent was removed to give the product in 90-95% yield. No melting-point depression was observed for a mixture of the product with a sample of the compound obtained by method A, and their IR spectra were identical.

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