SYNTHESIS OF 5(AND 6)-NITRO-4-METHYL-2,3-DIHYDRO-1H-1,5-BENZO-2-DIAZEPINONES

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The reaction of 4-nitro-o-phenylenediamine (I) with acetoacetic ester at room temperature under acid catalysis gives ethyl 3-(2-amino-5-nitrophenylamino)crotonate (II), which is readily cyclized to 7-nitro-4-methyl-2,3-dihydro-1H-1,5-benzo-2-diazepinone (III) on heating with alkaline agents. The reaction of I with acetoacetic ester in refluxing xylene gives isomeric 8-nitro-4-methyl-2,5-dihydro-1H-1,5-benzo-2-diazepinone (IVa) or 8-nitro-4-methyl-2,3-dihydro-1H-1,5-benzo-2-diazepinone (IVb), which are readily interconverted. The synthesis of IV is complicated by the side formation of 5-nitro-2-methylbenzimidazole (V) and thermal rearrangement of IVa and IVb to 5-nitro-1-isopropenylbenzimidazolone (VI). 6-Nitro-1-isopropenylbenzimidazolone (VII) is similarly obtained on heating III.

It has been demonstrated [1] that 4-methyl-o-phenylenediamine reacts with acetoacetic ester (AE) under mild conditions to give the arylaminocrotonate through the more basic amino group. This crotonate undergoes closure to a seven-membered ring under more severe conditions to form 4,8-dimethyl-2,3-dihydro-1H-1,5-benzo-2-diazepinone. If the process is carried out with strong heating right from the start, the isomeric 4,7-dimethyl-2,3-dihydro-1H-1,5-benzo-2-diazepinone is formed, but the synthesis is complicated by rearrangement with ring contraction to give a benzimidazole derivative [2].

In the present research we have made a similar investigation by introducing a strongly electron-acceptor group rather than an electron-donor methyl group into the benzene ring, and this made it possible to expect the formation of primarily the 4,7-isomer under mild conditions (where the rearrangement processes are not yet realized). Our experiments confirmed that diamine I reacts with acetoacetic ester at room temperature under the influence of acid catalysis to give crotonate II. A triplet (1.02 ppm) and a quartet (4.0 ppm) of an ethyl group are seen in the PMR spectrum of II. A broad singlet (due to an allyl interaction) of the protons of a methyl group (1.64 ppm) and a singlet of a vinyl proton (4.75 ppm) at strong field are also present, and this confirms the enamine structure of the crotonate.

Crotonate II is quite readily cyclized on heating, especially in the presence of sodium ethoxide, to 7-nitro-4-methyl-2,3-dihydro-1H-1,5-benzo-2-diazepinone (III). When the latter is heated to 220-230°, it is isomerized to 6-nitro-1-isopropenylbenzimidazolone (VII). Acid hydrolysis of VII gives the previously described [3, 4] 5-nitrobenzimidazolone (VIII). The PMR spectrum of diazepinone III contains singlets of methyl (2.93 ppm) and methylene (3.93 ppm) groups and signals of the protons of a benzene ring (7.50-8.47 ppm), which confirms structure III.

When I and AE are heated in a large amount of xylene, the chief product is 8-nitro-4-methyl-2,5-dihydro-1H-1,5-benzo-2-diazepinone (IVa). If the amount of solvent is halved, the yield of diazepinone IVa is reduced by 30%, diazepinone III is formed in low yield (2-3%), and 11% crotonate II and 38% 2-methyl-6-nitrobenzimidazole (V) are obtained. Diazepinone IVa is isolated from dilute solutions in xylene or acetone as a yellow crystalline substance. However, if the crystallization is carried out with a concentrated solution, a bright-red substance (IVb) is precipitated; this substance is converted to IVa in acetone and pyridine solutions. Substances IVa and IVb have the same elementary composition and melting points (197-197.5°)

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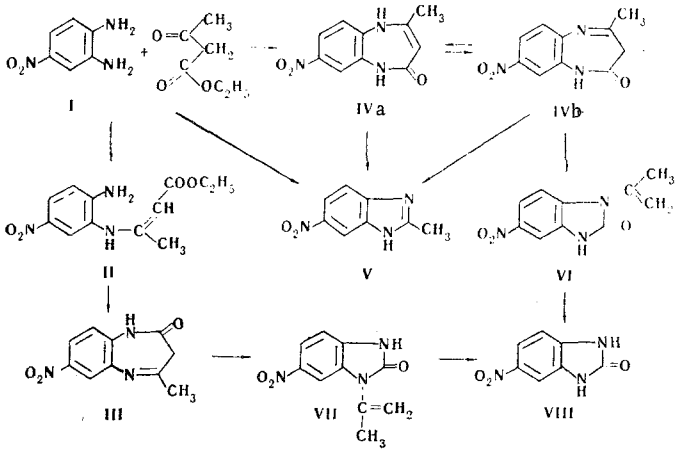

and behave identically during chromatography on a thin layer of aluminum oxide. The UV spectra of IVa and IVb in dimethylformamide are identical but differ from the UV spectrum of diazepinone III (Fig. 1) in that the long-wave band in the spectrum of IVa undergoes a bathochromic shift and is of high intensity, which is explained by the opposite effects of the NO_2 and $-NH-$ groups on the conjugated system of the molecule, in which the donor ($-NH-$) and acceptor (NO_2) substituents are para to one another. Refluxing IVa and IVb with dilute acids causes cleavage of the seven-membered ring to give 2-methyl-5-nitro-2-benzimidazolone (V), which is also formed quantitatively on heating I and AE to 180°. The thermal rearrangement of benzodiazepinones IVa and IVb leads to the formation of the same 1-isopropenylbenzimidazolone (VI), which, like VII, is converted to 5-nitrobenzimidazolone (VIII) on heating with acids.

The isomeric 5(and 6)-nitro-1-isopropenylbenzimidazolones (VI and VII) have three absorption maxima at 224, 251-253, and 338 nm in their UV spectra (Fig. 2). The high intensity of the long-wave band of VI is explained by the different positions of the isopropyl and nitro groups in VI and VII. The PMR spectra of VI and VII contain singlets of methyl groups at 2.10 and 2.16 ppm, which are broadened due to the allyl interaction with the protons of the vinyl group. The signals of the vinyl protons of VII (5.06 and 5.13 ppm) undergo a diamagnetic shift as compared with the position of the signals for the vinyl protons of imidazolone VI (5.10 and 5.26 ppm), which is evidently due to the different orientation of the isopropyl group relative to the benzene ring.

Thus the condensation of diamine I with AE proceeds specifically to a considerably greater degree than was observed for 4-methyl-o-phenylenediamine. The influence of a nitro group is exerted substantially in the facile shift of the double bond in IV and facilitates isomerization to benzimidazolone derivatives VI and VII.

EXPERIMENTAL

The PMR spectra of pyridine and trifluoroacetic acid solutions were recorded with an RS-60 spectrometer with hexamethyldisiloxane as the external standard. The selection of the reaction conditions and monitoring of the individuality of the substances was accomplished by means of chromatography in a thin layer of aluminum oxide [chloroform–alcohol (20:1)].

Ethyl 3-(2-Amino-5-nitrophenylamino)crotonate (II). Two drops of concentrated hydrochloric acid were added to a mixture of 3.06 g (0.01 mole) of 4-nitro-1,2-phenylenediamine (I) [5] and 12 ml (0.1 mole) of AE, and the mixture was stirred at room temperature for 20-30 min. The liquid mixture gradually began to solidify. The solid mass was washed with ether to give 4.85 g (91%) of II with mp 138-139° (from ether–petroleum ether). Ester II was a light-yellow crystalline substance that was quite soluble in the cold in acetone, dioxane, chloroform, and dichloroethane, as well as in hot alcohols, benzene, and ether. Found: C 53.9; 54.0; H 5.5; 5.6%. $C_{12}H_{15}N_3O_4$. Calculated: C 54.3; H 5.7%.

7-Nitro-4-methyl-2,3-dihydro-1H-1,5-benzo-2-diazepinone (III). A mixture of 2.9 g (0.011 mole) of crotonate II and sodium ethoxide (from 0.49 g of sodium and 20 ml of ethanol) was heated on a water bath for 30 min. The mixture was then cooled, 20 ml of water was added, and the aqueous mixture was neutralized with acetic acid to precipitate the product. The precipitate was removed by filtration to give 1.7 g (71%) of a product with mp 227-228° (from dimethylformamide). Found: C 55.0; 54.9; H 4.4; 4.1; N 19.1; 18.8%. $C_{10}H_9N_3O_3$. Calculated: C 54.8; H 4.1; N 19.2%.

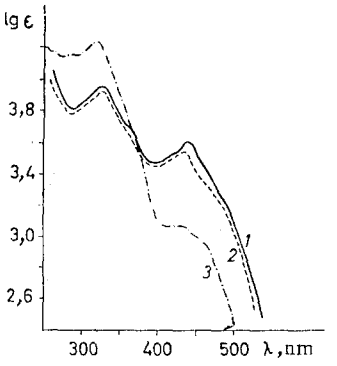

Fig. 1. UV spectra of 5 (and 6)-nitro-4-methyl-1,5-dibenzo-2-diazepinones: 1) IVa; 2) IVb; 3) III.

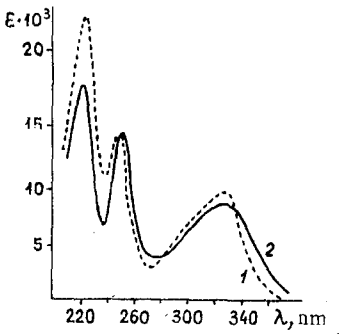

Fig. 2. UV spectra of isopropenyl-2-benzimidazolones: 1) VI; 2) VII.

Condensation of 4-Nitro-1,2-phenylenediamine with Acetoacetic Ester. A. A solution of 1.76 ml (0.014 mole) of acetoacetic ester in 40 ml of xylene was added dropwise in the course of 2 h to a heated mixture of 2 g (0.013 mole) of 4-nitro-o-phenylenediamine in 300 ml of xylene. The mixture was heated with a water separator for 6 h. A total of 240 ml of xylene was removed by distillation, and the residue was cooled to precipitate 2.4 g (88%) of 8-nitro-4-methyl-2,3-dihydro-1H-1,5-benzo-2-diazepinone (IVa) with mp 197-197.5° (from acetone). Benzodiazepinone IVa was only slightly soluble in the cold in chloroform, benzene, ether, and hexane. Found: C 54.9; 55.0; H 4.2; 4.1; N 19.7; 19.0%. $C_{10}H_9N_3O_3$. Calculated: C 54.8; H 4.1; N 19.2%.

When IVa or the reaction product was crystallized from concentrated alcohol solution, bright-red 8-nitro-4-methyl-2,3-dihydro-1H-1,5-benzo-2-diazepinone (IVb) with mp 196-197° was obtained. Found: C 54.7; 54.8; H 4.2; 4.3; N 19.8; 19.1%. $C_{10}H_9N_3O_3$. Calculated: C 54.8; H 4.1; N 19.2%.

B. A mixture of 6.12 g (0.04 mole) of I and 7.6 ml (0.06 mole) of acetoacetic ester in 500 ml of xylene was heated with a water separator for 4 h. The mixture was cooled, and the precipitate was removed by filtration to give 5.9 g (67%) of a substance, which was washed with three portions of hot alcohol to give 3.5 g (40%) of IVa. The residue left after removal of the alcohol was crystallized from dimethylformamide to give 0.2 g of III with mp 227-228°. The addition of water to the dimethylformamide precipitated 2.4 g (38%) of 2-methyl-6-nitrobenzimidazole (V) with mp 222-224° (221° [3]). The picrate had mp 201° (201° [3]). Vacuum evaporation of the xylene solution with a water aspirator gave 1.1 g (11%) of ester II with mp 138-139°.

6-Nitro-1-isopropenyl-2-benzimidazolone (VII). A 0.219 g (0.001 mole) sample of benzodiazepine III was heated at 220-230° for 15 min to give 0.216 g (98%) of VII with mp 229-230° (from aqueous alcohol). Found: C 55.2; H 3.8%. $C_{10}H_9N_3O_3$. Calculated: C 54.8; H 4.1%.

5-Nitro-1-isopropenyl-2-benzimidazolone (VI). A 0.2 g (0.001 mole) sample of benzodiazepine IV was heated at 185-189° for 20 min. Cooling of the mixture gave 0.19 g (95%) of VI with mp 244-245° (from aqueous alcohol). Found: C 54.4; 54.6; H 4.6; 4.8%. $C_{10}H_9N_3O_3$. Calculated: C 54.8; H 4.1%.

5(6)-Nitrobenzimidazolone (VIII). A 0.2 g (0.001 mole) sample of isopropenylbenzimidazolone VI or VII was refluxed with 3 ml of 2 N hydrochloric acid for 1.5 h. The mixture was then cooled and neutralized with ammonium hydroxide to give 0.12 g (75%) of VIII with mp 307° (306° [3]). The product did not depress the melting point of 5-nitrobenzimidazolone obtained from 4-nitro-o-phenylenediamine and urea [3].

5-Nitro-2-methylbenzimidazole (V). A. A mixture of 0.42 g (0.002 mole) of benzodiazepine III or IV and 8 ml of 2 N sulfuric acid was refluxed for 30 min. Neutralization of the mixture with 2 N NaOH gave 0.17 g (50%) of V with mp 222° (from water) (221° [6]).

B. A mixture of 1.53 g (0.01 mole) of diamine I and 1.95 ml (0.015 mole) of AE was heated to 180° for 20 min. The melt was cooled and washed with ether to give 2.05 g (98%) of V with mp 222-224°. The product did not depress the melting point of the benzimidazole obtained in experiment A.

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