REACTION OF 4-METHYL-1,2-PHENYLENEDIAMINE WITH ACETOACETIC ESTER

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Depending on the reaction conditions, 4-methyl-1,2-phenylenediamine reacts with acetoacetic ester to form 4,7(or 8)-dimethyl-2,3-dihydro-1H-1,5-benzodiazepinones or 5(or 6)-methyl-1-isopropenylbenzimidazolones. During acid catalysis under mild conditions, the more basic diamine group initially reacts with acetoacetic ester to form ethyl 3-(2-amino-4-toluidino)-crotonate, which subsequently can be converted to the corresponding benzodiazepinone and 2,5-dimethylbenzimidazole.

The reaction of β-keto esters with aromatic diamines has been studied in quite some detail in the case of o-phenylenediamine [1-3]. It has been shown that dihydrobenzo-2-diazepinones and, in the case of acetoacetic ester (AAE), 1-isopropenyl-2-benzimidazolone are formed in neutral and alkaline media [2, 3]. The formation of arylaminocrotonates and 3-alkyl- or 3-arylbenzimidazoles is observed in acidic media [1]. According to the data in [4], however, 2-(trifluoroacetonyl)benzimidazole was obtained as the chief product from the reaction of trifluoroacetoacetic ester with o-phenylenediamine in acid media. A similar structure for ketones of the benzimidazole series was assigned, without special proof, to the substances formed in the reaction of 1,2- and 2,3-naphthylenediamines with acetoacetic and benzolyacetic esters [5, 6].

In the case of diamines that have nonequivalent amino groups, one can expect the formation of two isomeric dihydrobenzodiazepinones or a process that favors one of the isomers. In fact, 2,3-diaminopyridine reacts with AAE to form a rather complex mixture of products [7-9]. However, it is possible that this is in some measure determined by the specifics of the pyridine component. On the basis of general concepts regarding the trend of this reaction, it was assumed that the first act in the reaction is the formation of the corresponding arylaminocrotonic ester, which subsequently cyclizes to a dihydrobenzodiazepinone. Moreover, the more basic amino group participates in the formation of the ester [7-9].

This assumption compelled us to study this reaction in the case of a simple model – 4-methyl-1,2-phenylenediamine. In the course of our experimentation, Acheson and Tully published a paper [10] in which they reported the similar condensation of 4-chloro-1,2-phenylenediamine with AAE and concluded that the formation of the arylaminocrotonic ester proceeds at the expense of the less basic rather than the more basic amino group. However, they did not vary the conditions and did not search for isomeric substances.

We were able to show that the reaction of 4-methyl-1,2-phenylenediamine with AAE under the mildest conditions in neutral media or in the presence of small amounts of acid yields ethyl 3-(2-amino-4-toluidino)-crotonate (V), the UV spectrum of which is extremely similar to the spectrum of ethyl 3-(2-aminoanilino)-crotonate [3].

The PMR spectrum of crotonate V contains signals from the protons of an ethyl group (triplet at 1.17 and quartet at 3.88 ppm), singlets from methyl groups (1.6 and 2.06 ppm), a broad signal from NH protons (9.42 ppm), and a signal from a proton attached to a vinyl group (4.44 ppm). The latter is evidence that the double bond is not shifted to the nitrogen atom. There are signals in the aromatic proton region at 6.26, 6.60, and 6.66 ppm.

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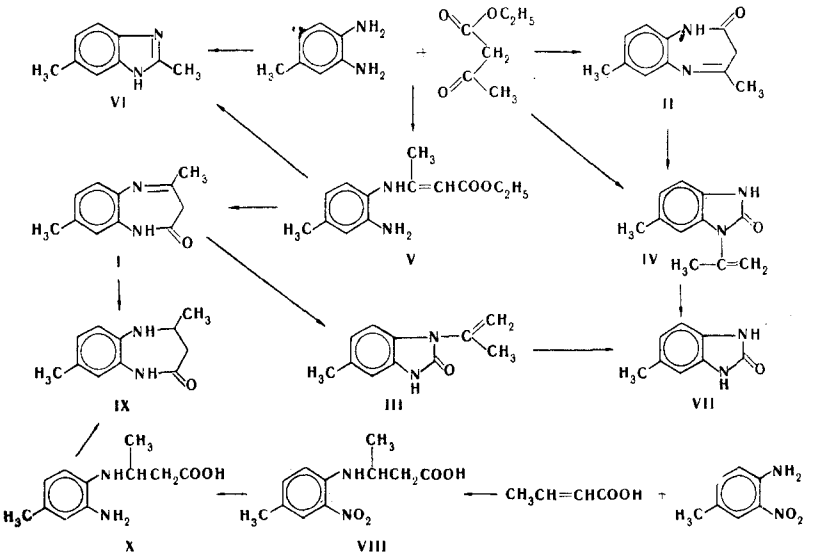

When crotonate V is heated in the presence of sodium ethoxide via the method in [2], it is converted to compound I with mp 174-175° C and empirical formula $C_{11}H_{12}N_2O$ (see the above scheme). Compound I is rearranged to another substance (III) of the same composition with mp 159-160° C on heating at 155-160° C for 2 h. The latter is converted to the known [11, 12] 5-methyl-2-benzimidazolone (VII) on heating with dilute hydrochloric acid. The PMR spectrum of III contains signals from two methyl groups (2.23 and 2.28 ppm), an unresolved multiplet from methylene protons (5.22 ppm), and signals from aromatic protons (6.65, 6.84, and a doublet at 6.89 ppm). On the basis of these results, the 5-methyl-1-isopropenyl-2-benzimidazolone structure can be assigned to substance III. The presence of an enamine grouping in III explains its ease of conversion to the corresponding imidazolone (VII). Isopropenylbenzimidazolones are usually formed during the thermal rearrangement of dihydro-1,5-benzodiazepinones [2, 7]. This was the basis for assuming the 4,8-dimethyl-2,3-dihydro-1H-1,5-benzo-2-diazepinone structure for I. The synthesis of compounds with the same physical constants was described in 1970 by Japanese chemists [13] from 4-methyl-1,2-phenylenediamine and diketene. However, the structure of I was not established, and two possible positions (7 or 8) were only conjecturally proposed for the methyl group.

The PMR spectrum of diazepinone I in pyridine contains signals from two methyl groups (2.17 and 2.20 ppm) and a signal from methylene protons (3.18 ppm), which does not contradict our assumed structure. However, in order to establish the position of the substituent in the benzene ring and to more accurately prove the structure of I, we accomplished the alternative synthesis of this compound by heating 2-nitro-4-toluidine with crotonic acid via the method in [10] to give 3-(2-nitro-4-toluidino)butyric acid (VIII). The reductive cyclization of VIII under mild conditions resulted in the formation of 2,3,4,5-tetrahydro-1H-1,5-benzo-2-diazepinone (IX), which was also obtained by the catalytic hydrogenation of dihydrodiazepine I. Thus it can be assumed that, under the conditions that we selected, the more basic amino group of the aromatic diamine reacts during the formation of the arylaminocrotonate in the reaction with AAE under mild conditions, and this also subsequently determines the position of the substitutent in the benzene ring of the oxobenzodiazepine.

The situation is different if the condensation is carried out by heating the starting substances in refluxing xylene. Two substances with mp 165-166° C (II) and 125-126° C (IV), which have the same composition as I and II, are isolated from the reaction of the diamine with AAE. The amounts of substances formed depend on the heating time and the degree of dilution of the solution. When the reaction is carried out in very dilute solutions, II is formed in 80% yield, while only traces of IV are formed. Raising the reagent concentrations leads to a decrease in the yield of II and to an increase in the yield of IV. An increase in the heating time also promotes an increase in the yield of IV. Like diazepinone I, II is converted to IV on heating, and the acid cleavage of IV leads to 5-methyl-2-benzimidazolone (VII). On the basis of this, the 4,7-dimethyl-2,3-dihydro-1H-1,5-benzo-2-diazepinone structure can be assigned to II, and the 5-methyl-3-isopropenyl-2-benzimidazolone structure can be assigned to IV.

If the starting substances are heated in the absence of a solvent at 100 or 180° C, the major product proves to be 2,5-dimethylbenzimidazole (VI), which is also formed during the recrystallization of crotonate V from water. This sort of formation of 2-methylbenzimidazole from the corresponding crotonate was also described in [14].

Thus the more basic amino group of the aromatic diamine reacts with the keto group of AAE under mild conditions, especially under the influence of an acid catalyst. The aminocrotonic ester that is formed is cyclized on heating to 2-methylbenzimidazole or dihydrobenzodiazepinone, while the latter is converted to 1-isopropenyl-2-benzimidazolone under more severe conditions. If the condensation is carried out all at once under severe conditions, then, as in the Conrad–Limpach synthesis, the arylaminocrotonate is isomerized to an amide of acetoacetic acid [15, 16] with simultaneous (or subsequent) cyclization leading to the dihydrobenzodiazepinone and the 1-isopropenylbenzimidazolone of isomeric structure.

EXPERIMENTAL

The purity of the substances was monitored by chromatography in a thin layer of aluminum oxide. The PMR spectra of pyridine and chloroform solutions were recorded with an RS-60 spectrometer with hexamethyldisiloxane as the internal standard. The UV spectra of 96% alcohol solutions were recorded with an SF-4A spectrophotometer.

Ethyl 3-(2-Amino-4-toluidino)crotonate(V). 4-Methyl-1,2-phenylenediamine [17] [3.66 g (0.03 mole)] was mixed with 4.56 ml (0.036 mole) of acetoacetic ester. The diamine dissolved at the outset, and the mixture solidified after 20-30 min to give 6.73 g (96%) of colorless cyrstals of crotonate V with mp 82-83° C. The product was soluble in alcohols, chloroform, ether, acetone, and benzene, hot water, and hot petroleum ether. UV spectrum: λ_{max} 242, 288 nm, log ε 4.08 and 4.27. Found: C 66.9; H 7.6; N 12.3%. $C_{13}H_{18}N_2O_2$. Calculated: C 66.7; H 7.7; N 12.0%.

4,8-Dimethyl-2,3-dihydro-1H-1,5-benzo-2-diazepinone (I). A mixture of 5.85 g (0.025 mole) of crotonate V and sodium ethoxide (from 0.58 g of sodium and 25 ml of alcohol) was refluxed for 1 h, and evaporated to dryness. The residue was diluted with 50 ml of water and neutralized with acetic acid to pH 6 to give 3.1 g (66%) of a product with mp 174-175° C (from benzene–petroleum ether) (mp 174-175° C [13]). Found: C 70.5; H 6.5; N 15.3%. $C_{11}H_{12}N_2O$. Calculated C 70.2; H 6.4; N 14.9%.

5-Methyl-1-isopropenyl-2-benzimidazolone (III). A 1.41-g (0.0075 mole) sample of diazepinone I was heated at 155-160° C for 2 h. The product was dissolved in ether, and the ether was removed to give 1.25 g (89%) of III with mp 159-160° C (from aqueous ethanol). Found: C 70.1; H 6.3; N 15.1%. $C_{11}H_{12}N_2O$. Calculated: C 70.2; H 6.4; N 14.9%.

5-Methyl-2-benzimidazolone (VII). A) A mixture of 0.56 g (0.003 mole) of benzimidazolone III and 10 ml of 2 N hydrochloric acid was refluxed for 1 h, cooled, and neutralized to pH 8 with ammonium hydroxide. The resulting precipitate was removed by filtration and washed with water to give 0.42 g (95%) of a product with mp 297-298° C (after sublimation) (mp 293-296° C [11] and 302-304° C [12]).

B) Similarly, 0.42 g (95%) of VII with mp 297-298° C (after sublimation) was obtained from 0.56 g (0.003 mole) of benzimidazolone IV. Imidazolone VII did not depress the melting point of the substance obtained in Method A nor that of a sample synthesized from the diamine and urea via the method in [12].

3-(2-Nitro-4-toluidino)butyric Acid (VIII). A mixture of 4.56 g (0.03 mole) of 3-nitro-4-toluidine and 10.3 g (0.12 mole) of crotonic acid was heated at 160° C for 18 h. The mixture was cooled, and 100 ml of 2 N sodium hydroxide was added. The insoluble solid was removed by filtration, and the filtrate was diluted with a tenfold quantity of water and acidified to pH 6 with concentrated hydrochloric acid to give an orange precipitate of acid VIII. This was removed by filtration and washed with water to give 4 g (56%) of a product with mp 134-135°C (from aqueous alcohol). Found: N 12.0%. $C_{11}H_{14}N_2O_4$. Calculated N 11.8%. The product was soluble in alcohol, chloroform, ether, benzene, hot water, and hot carbon tetrachloride.

4,8-Dimethyl-2,3,4,5-tetrahydro-1H-1,5-benzo-2-diazepinone (IX). A) A mixture of 0.47 g (0.025 mole) of benzodiazepinone I in 20 ml of absolute ethanol was hydrogenated at room temperature over Raney nickel. The calculated amount of hydrogen was absorbed in 7-8 h. The solution was filtered, the alcohol was removed in vacuo, and the residual, colorless solid was crystallized from benzene–petroleum ether to give 0.42 g (87%) of IX with mp 196-197° C. Found: C 69.0; H 7.5; N 15.0%. $C_{11}H_{14}N_2O$. Calculated: C 69.5; H 7.4; N 14.7%.

B) A mixture of 1.2 g (0.005 mole) of 3-(2-nitro-4-toluidino)butryic acid in 50 ml of absolute ethanol was similarly reduced. The alcohol was removed, the residue was dissolved in 120 ml of water, and 2.5 ml of concentrated hydrochloric acid was added. The mixture was refluxed for 30 min on a water bath, cooled, and neutralized with 2N sodium hydroxide to give 0.43 g of IX. Evaporation of the filtrate and extraction with benzene gave an additional 0.27 g of product for an overall yield of 70% of a substance with mp 196-

197° C. The product did not depress the melting point of IX obtained in Method A. Both substances had R_f 0.40 [chloroform–ethanol (20:1)].

3-(2-Amino-4-toluidino)butyric acid (X). A mixture of 1.2 g (0.005 mole) of VIII in 50 ml of ethanol was similarly reduced. The alcohol was removed, and the residue was crystallized from benzene–petroleum ether to give 0.95 g (91%) of X with mp 121-122° C. Found: N 13.7%. $C_{11}H_{16}N_2O_2$. Calculated: N 13.5%.

4,7-Dimethyl-2,3-dihydro-1H-1,5-benzo-2-diazepinone (II). A heated solution of 4.56 ml (0.036 mole) of AAE in 50 ml of xylene was added dropwise to a refluxing solution of 3.66 g (0.03 mole) of diamine in 500 ml of xylene, and the mixture was refluxed with water separation for 1 h. A total of 15 ml of an azeotropic mixture of alcohol, water, and xylene was separated. The xylene was removed to give 4.55 g (87%) of diazepine II with mp 164-165° C (from benzene–petroleum ether). Found: C 70.5; H 6.5; N 15.1%. $C_{11}H_{12}N_2O$. Calculated C 70.2; H 6.4; N 14.9%.

Condensation of 4-Methyl-1,2-phenylenediamine with Acetoacetic Ester. A solution of 7.8 ml (0.06 mole) of AAE in 10 ml of xylene was added dropwise to a refluxing solution of 6.1 g (0.05 mole) of diamine in 50 ml of xylene, and the mixture was refluxed with water separation for 1 h. It was then cooled and poured into 70 ml of 20% sodium hydroxide and the mixture was stirred at 10° C for 15 min. The resulting precipitate was removed by filtration, diluted with water, and neutralized with glacial acetic acid. The resulting substance was washed with water to give 1.68 g (18%) of 5-methyl-1-isopropenyl-2-benzimidazolone (IV) with mp 125-126° C (from water) that was identical to the benzimidazolone obtained by the thermal rearrangement of II. Isopropenylbenzimidazolones III and IV are soluble in alcohols, acetone, chloroform, benzene, carbon tetrachloride, and hot water, and insoluble in hexane and petroleum ether.

The aqueous alkaline layer was separated from the xylene, cooled, and neutralized with acetic acid to pH 6-7 to give 4 g (42%) of 4,7-dimethyl-2,3-dihydro-1H-1,5-benzo-2-diazepinone (II), which was identical to the II obtained in a large volume of xylene. Diazepines I, II, and IX are soluble in alcohols, acetone, chloroform, hot water, hot benzene, and hot carbon tetrachloride, and insoluble in ether, hexane, and petroleum ether.

The xylene solution was washed several times with water, dried over $MgSO_4$, and evaporated to dryness to give 1.78 g (15%) of V, which was identical to the acid obtained above.

6-Methyl-1-isopropenyl-2-benzimidazolone (IV). A 0.38-g (0.002 mole) sample of diazepinone II was heated at 125-130° C for 2 h and cooled. The melt was dissolved in 6 ml of 20% sodium hydroxide, and the solution was filtered. The insoluble solid was dissolved in water and neutralized to pH 6 with acetic acid to precipitate 0.2 g (52%) of IV with mp 125-126° C (from water). Found: C 70.1; H 6.4; N 14.7%. $C_{11}H_{12}N_2O$. Calculated: C 70.2 H 6.4; N 14.9%.

2,5-Dimethylbenzimidazole (VI). A mixture of 2.44 g (0.02 mole) of diamine and 3.04 ml (0.024 mole) of AAE was held on a boiling-water bath for 3 h. It was then washed with ether to give 2.3 g (79%) of VI with mp 203-204° C (from water) (mp 203° C [18]).

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