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Condensation of 3-nitro-1,2-phenylenediamine with ethyl acetoacetate in boiling xylene gave two isomeric 2,3-dihydro-4-methyl-9-nitro- and 2,5-dihydro-4-methyl-6-nitro-1*H*-1,5-benzodiazepin-2-ones, the 9-nitro derivative thermal rearrangement product *N*-isopropenyl-4-nitrobenzimidazolone and a non cyclic acetoacetamide derivative. At room temperature these reactants afforded 2,3-dihydro-2-ethoxycarbonyl-methyl-2-methyl-4-nitrobenzimidazole.

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In recent years, increasing attention has been directed towards imidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one derivatives due to their antiviral activity against HIV-1 [1]. One aspect of our current interests is to develop novel tricyclic structural analogs based on [1,5]benzodiazepine. In this context we required, as intermediates, the nitro-substituted dihydro-1,5-benzodiazepin-2-ones bearing a nitro group on their C-9 or C-6 positions. One route to the synthesis of the desired heterocycles includes the method when an aromatic ring substituent is present already in the starting material. In this paper, we describe our studies on the reaction of 3-nitro-1,2-phenylenediamine **1** with ethyl acetoacetate **2** leading to the desired nitrobenzodiazepinones and provide evidence of the formation of various products depending upon the reaction conditions.

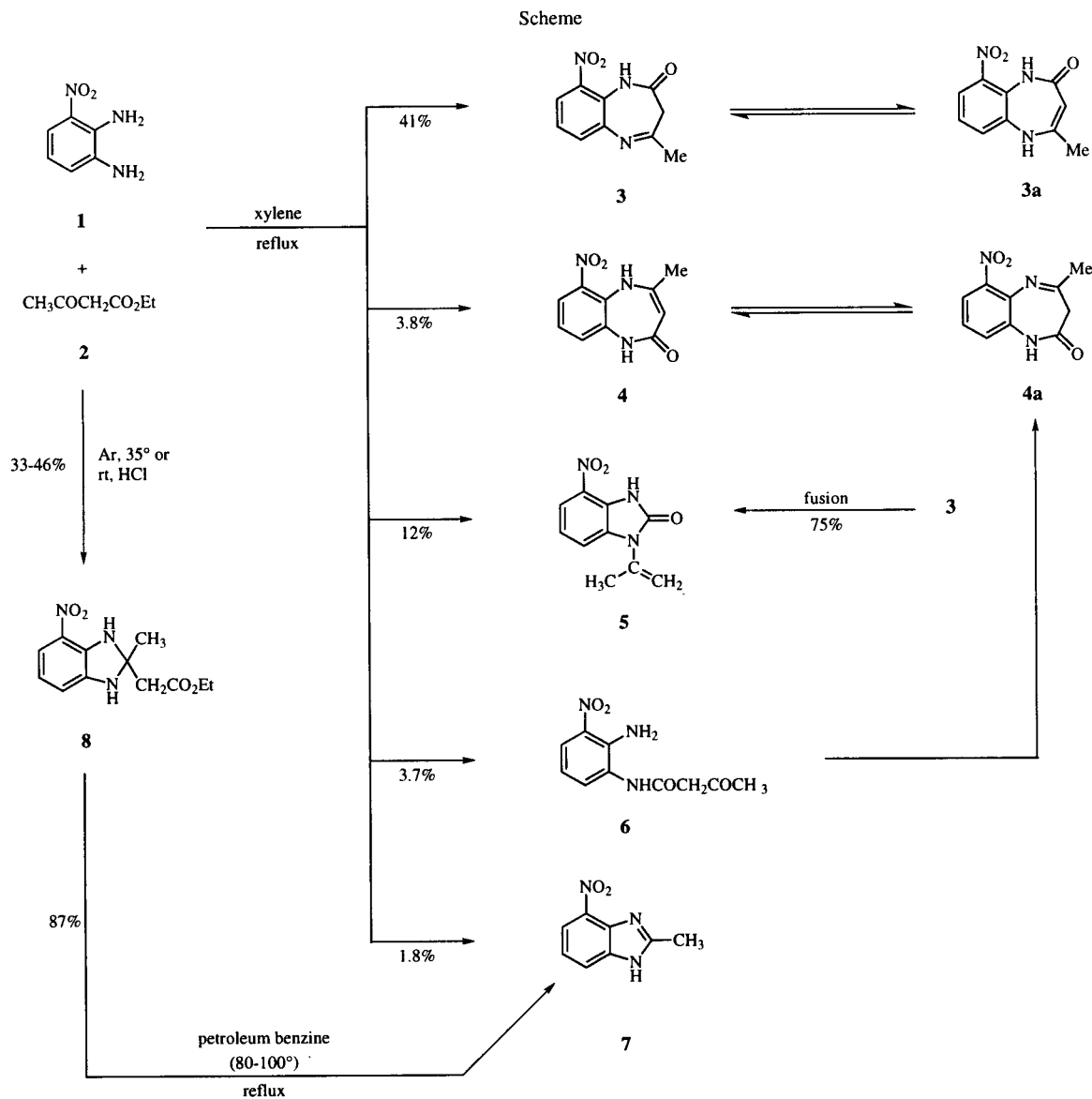
Thus, *ortho*-diamine **1** and β -ketoester **2** were condensed in boiling xylene with azeotropic removal of water and ethanol. The reaction afforded 9-nitro-1,5-benzodiazepinone **3**, as the main product, and the isomeric 6-nitro derivative **4** together with *N*-isopropenylbenzimidazolone **5**, acetoacetamide derivative **6** and 2-methyl-4(7)-nitrobenzimidazole **7** (Scheme). Structural assignments of diazepinones **3** and **4** implies the condensation of the ketocarbonyl function of the β -ketoester with the more basic 1-amino group of diamine **1** (compound **3**), whereas the alternate structure **4** implies the reaction of the carboxy function with this amino group. On the other hand, we have shown the existence of the interconvertible prototropic tautomers **3a** and **4a**. It was established upon crystallization of **3** from methanol leading to the **3a**. The fact, that condensed dihydrodiazepinones can exist in the stable tautomeric forms has been previously noted [2-4]. The tautomers **3**, **3a** exhibited different melting points and unique uv, ir and ¹H nmr spectra. The ¹H nmr spectrum of **3** in deuteriochloroform revealed the presence of a methylene group giving rise to a singlet at 3.16 ppm. The spectrum of freshly prepared solution of **3** in dimethyl-*d*₆ sulfoxide also confirmed this structure, however, after storage overnight at 35° the two tautomeric species **3** and **3a**

were observed in approximate 3:2 ratio. The presence of **3a** was confirmed by the appearance of C=CH proton multiplet signal at 4.61 ppm and of additional NH proton signal. Tautomeric equilibrium **3a** \leftrightarrow **3** (2:3) was also detected upon storage of the **3a** solution in the same deuterated solvent. In a similar manner an enamine structure of the isomeric 6-nitro derivative **4** and formation of tautomeric form **4a**, which was demonstrable only in this polar solvent, have been confirmed.

The facile thermal conversion of condensed dihydro-1,5-diazepinones into *N*-alkenylbenzimidazolones has been previously described [2,4]. This rearrangement reaction has been adapted for the elucidation of the structures of ambiguous diazepinone derivatives. Therefore, in our case, the formation of **5** as a by-product was expected. Compound **5** was also obtained by dry fusion of **3**. The structural relationship between the benzimidazolone **5** and the diazepinone **3** from which it is derived provides reasonable confirmation for the structure of **3**.

It appears that a rather high reaction temperature favors the formation of amide **6**. A similar acetoacetamide derivative was obtained by heating 4,5-diaminopyrimidine with an excess of **2** [3]. In the ¹H nmr spectrum of **6** the presence of a one proton triplet signal with a chemical shift at 6.65 ppm (*J* = 8.0 Hz) was assigned to the aromatic proton attached at C-5. This is in accordance with the influence of electron-donating *para*-amino group on the shielding of this proton. This promoted result allied to the fact that an amide **6** structure was constituted from the reaction of the more basic amino function of **1** with the carboxy group of **2**. Further evidence of this assumption was given when the solution of **6** in dimethyl-*d*₆ sulfoxide was kept at 90° for 14-15 hours and the cyclization product **4a** (~60%) was identified by ¹H nmr.

An alternate way to the synthesis of dihydrodiazepinones can be realized from aminocrotonate intermediates by subsequent conversion to seven-membered heterocycles [2,3,5]. We attempted the reaction of **1** and **2** under argon at 35° and at room temperature in the presence of a



trace of concentrated hydrochloric acid. However, both experiments resulted in dihydrobenzimidazole **8**. In the ^1H NMR spectrum of **8** two singlet signals with chemical shifts at 1.67 ppm and at 2.82 ppm were assigned to the methyl and methylene protons, respectively, and two broad signals at 4.84 ppm and 7.02 ppm for protons, that exchange with deuterium oxide, confirmed the presence of two different NH groups. The IR spectrum showed a strong carbonyl absorption at 1720 cm^{-1} , a sharp band at 3354 cm^{-1} and a broader band at 3280 cm^{-1} , both typical of N-H vibrations. The spectrum of **8** in a chloroform solution exhibited only one band at 3420 cm^{-1} . If an NH_2 group had been present, two peaks (symmetrical and asymmetrical NH_2 stretching vibrations) would have been found in

the spectrum [6]. These observations allow us to assign the dihydrobenzimidazole structure for **8**.

The analogous products such as **7** which were isolated from the reaction mixture were obtained previously. Contraction to a benzimidazole derivative has been observed when various *ortho*-diamines were condensed with ethyl acetoacetate [7] or, especially, with 2-alkyl-substituted derivatives of this ester [4]. The presumption was made that the formation of 2-methylbenzimidazole derivatives proceeds through the *gem*-substituted dihydrobenzimidazolium salts followed by elimination of an ester molecule [4]. In our case, the prolonged refluxing of **8** in the petroleum benzene (80-100°) afforded **7**. In view of the above mentioned reports, the transformation of **8** into **7** was understandable.

EXPERIMENTAL

The uv spectra were obtained on a Specord UV VIS spectrometer in ethanol. The ir spectra were recorded on a Specord 75 IR spectrometer. The ^1H nmr spectra were recorded in deuteriodimethyl sulfoxide on a Hitachi R-22 (90 MHz) instrument at 35° and chemical shifts (δ) are expressed in ppm relative to the internal standard hexamethyldisiloxane. Ascending tlc was performed on silica gel plates *Silufol* UV₂₅₄ (chloroform-ethyl acetate-methanol, 14:7:1). Melting points were determined in open capillaries and are uncorrected. 3-Nitro-1,2-phenylenediamine was synthesized by selective catalytic hydrogenation of 2,6-dinitroaniline.

Reaction of 3-Nitro-1,2-phenylenediamine with Ethyl Acetoacetate in Xylene.

To a solution of 4.6 g (30 mmoles) of 3-nitro-1,2-phenylenediamine **1** dissolved in 350 ml of dry refluxing *ortho*-xylene, a solution (70 ml) in the same warm solvent of ethyl acetoacetate **2** (4.75 g, 36 mmoles) was added dropwise during 45 minutes and the solution was maintained at reflux (about 3 hours) with continuously azeotropic removal (Dean-Stark trap) of water and ethanol. Then it was allowed to reach ambient temperature and allowed to stand overnight. The deposited crystalline material was filtered, washed with xylene (30 ml) and air-dried. This crude product (*ca.* 0.5 g) was dissolved in methanol (50 ml) under reflux and filtered hot. The filtrate was evaporated to 15 ml and ether (15 ml) was added. The precipitated solid was filtered to give 270 mg of **6**. The filtrate was evaporated to dryness. The residual thick dark slurry was purified by sublimation *in vacuo* affording 100 mg of **7**. The original xylene filtrate was evaporated *in vacuo* to *ca.* 70 ml and was allowed to stand in the refrigerator overnight. The precipitate which appeared was collected, washed with ether and air-dried. This crude product (2.2 g) was dissolved in refluxing benzene (30-40 ml). After standing at room temperature for 3 hours the precipitated solid **5** was filtered. The benzenic filtrate was evaporated to dryness leaving solid **3** (*ca.* 1.2 g) which was dissolved in 15 ml of chloroform and was allowed to stand to combine with the other portion of this compound. The addition of ether (70 ml) to the mother xylene filtrate afforded the precipitation of solid which was filtered. The crude product (2.0 g) was triturated with 30 ml of chloroform to give, after filtration, 250 mg of compound **4**. The combined chloroform solutions (45 ml) were treated with ether (45 ml). The solid which appeared was filtered and dried to give 2.7 g of **3**.

2,3-Dihydro-4-methyl-9-nitro-1*H*-1,5-benzodiazepin-2-one **3**.

This compound was obtained as orange needles (benzene) in 41% yield, mp 161-163 $^\circ$; R_f 0.62; uv: λ max 267 (log ϵ 3.88), 333 (log ϵ 3.52) nm; ir (potassium bromide): ν 3275 and 3150 (NH), 1690 (CO), 1640 (C=N), 1500 and 1340 (NO₂) cm^{-1} ; ir (chloroform): ν 3340 (NH), 1690 (CO) cm^{-1} ; ^1H nmr: δ 10.09 (s, 1H, NH), 7.92 (dd, 1H, H₈, J = 8.0, 2.0 Hz), 7.60 (dd, 1H, H₆, J = 8.0, 2.0 Hz), 7.37 (t, 1H, H₇, J = 8.0 Hz), 3.20 (s, 2H, CH₂), 2.32 (s, 3H, CH₃).

Anal. Calcd. for C₁₀H₉N₃O₃: C, 54.79; H, 4.14; N, 19.17. Found: C, 54.92; H, 4.16; N, 19.15.

2,5-Dihydro-4-methyl-9-nitro-1*H*-1,5-benzodiazepin-2-one **3a**.

This compound was obtained by dissolving of 60 mg of **3** in 0.7 ml of methanol with heating and the solution was refluxed for 1-1.5 minutes. Quickly the deep red crystals appeared which were filtered, washed with 2 ml of precooled methanol and air-dried yielding 45 mg of **3a** (75%), mp 172-174 $^\circ$; uv: λ max ~229 shoulder (log ϵ 4.20), 298 (log ϵ 3.79), ~357 shoulder (log ϵ 3.53) nm; ir (potassium bromide): ν 3430, 3380 and 3320 (NH), 1727 and 1684 (CO), 1643 (C=C), 1524 and 1330 (NO₂) cm^{-1} ; ^1H nmr: δ 8.69 (s, 1H, 5-NH or 1-NH), 8.60 (s, 1H, 1-NH or 5-NH), 7.60 (dd, 1H, H₈, J = 8.0, 2.0 Hz), 7.25-6.89 (m, 2H, H_{6,7}), 4.61 (m, 1H, CH), 1.96 (s, 3H, CH₃).

Anal. Calcd. for C₁₀H₉N₃O₃: C, 54.79; H, 4.14; N, 19.17. Found: C, 54.72; H, 4.21; N, 19.25.

2,5-Dihydro-4-methyl-6-nitro-1*H*-1,5-benzodiazepin-2-one **4**.

This compound was obtained as reddish yellow needles (benzene) in 3.8% yield, mp 205-206 $^\circ$; R_f 0.42; uv: λ max 244 (log ϵ 4.25), 305 (log ϵ 3.48), 424 (log ϵ 3.15) nm; ir (potassium bromide): ν 3310, 3250, 3175 and 3140 (NH), 1680 (CO), 1640 (C=C), 1500 and 1300 (NO₂) cm^{-1} ; ir (chloroform): ν 3370 (NH), 1690 (CO) cm^{-1} ; ^1H nmr: δ 9.08 (s, 1H, 1-NH), 8.34 (s, 1H, 5-NH), 7.60 (dd, 1H, H₇, J = 8.0, 2.0 Hz), 7.25-6.95 (m, 2H, H_{8,9}), 4.78 (m, 1H, CH), 1.95 (s, 3H, CH₃).

Anal. Calcd. for C₁₀H₉N₃O₃: C, 54.79; H, 4.14; N, 19.17. Found: C, 55.05; H, 4.18; N 19.27.

2,3-Dihydro-4-methyl-6-nitro-1*H*-1,5-benzodiazepin-2-one **4a**.

Evidence for the existence of this compound was observed in deuteriodimethyl sulfoxide in an nmr tube; ^1H nmr: δ 10.78 (s, 1H, NH), 7.80-7.56 (m, 1H, H₇), 7.49-7.35 (m, 2H, H_{8,9}), 3.25 (s, 2H, CH₂), 2.30 (s, 3H, CH₃).

1-Isopropenyl-4-nitrobenzimidazol-2-one **5**.

An analytical sample was obtained as yellow crystals (ethanol) in 12% yield, mp 204-205 $^\circ$; R_f 0.80; uv: λ max 238 (log ϵ 4.11), 303 (log ϵ 3.88) nm; ir (potassium bromide): ν 3150 (NH), 1730 (CO), 1625 (C=C), 1510 and 1320 (NO₂) cm^{-1} ; ^1H nmr: δ 11.83 (s, 1H, NH), 7.78 (dd, 1H, H₅, J = 8.0, 2.0 Hz), 7.41 (dd, 1H, H₇, J = 8.0, 2.0 Hz), 7.15 (t, 1H, H₆, J = 8.0 Hz), 5.45 (m, 1H, CH₂), 5.18 (m, 1H, CH₂), 2.12 (m, 3H, CH₃).

Anal. Calcd. for C₁₀H₉N₃O₃: C, 54.79; H, 4.14; N, 19.17. Found: C, 54.56; H, 4.22; N, 19.16.

3-Oxobutanoic Acid *N*-(2-Amino-3-nitrophenyl)amide **6**.

This compound was obtained as brown crystals (toluene) in 3.7% yield, mp 125-126 $^\circ$; R_f 0.28; ir (potassium bromide): ν 3460, 3345 and 3235 (NH), 1710 and 1660 (CO), 1627 (NH₂), 1520 and 1323 (NO₂) cm^{-1} ; ir (chloroform): ν 3460, 3370 and 3340 (NH), 1710 and 1690 (CO), 1620 (NH₂) cm^{-1} ; ^1H nmr: δ 9.48 (s, 1H, NH), 7.92 (dd, 1H, H₄, J = 8.2, 2.0 Hz), 7.46 (dd, 1H, H₆, J = 8.0, 2.0 Hz), 7.10 (s, 2H, NH₂), 6.65 (t, 1H, H₅, J = 8.0 Hz), 3.64 (s, 2H, CH₂), 2.24 (s, 3H, CH₃).

Anal. Calcd. for C₁₀H₁₁N₃O₄: C, 50.63; H, 4.67; N, 17.71. Found: C, 50.38; H, 4.88; N 17.53.

2-Methyl-4(7)-nitrobenzimidazole **7**.

This compound was obtained by sublimation (1 Torr) as sand colored crystals in 1.8% yield, mp 217 $^\circ$, (lit [8], mp 217 $^\circ$); R_f 0.32; ^1H nmr: 12.96 (s, 1H, NH), 8.04 (dd, 1H, H₅ or 7, J = 8.0, 2.0 Hz), 7.96 (dd, 1H, H₇ or 9, J = 8.0, 2.0 Hz), 7.32 (t, 1H, H₆, J = 8.0 Hz), 2.62 (s, 3H, CH₃).

1-Isopropenyl-4-nitrobenzimidazol-2-one **5** by Dry Fusion of **3**.

A test tube containing 200 mg (0.9 mmole) of 2,3-dihydro-4-methyl-9-nitro-1*H*-1,5-benzodiazepin-2-one **3** was plunged into a hot oil bath preheated to 150°. When the temperature was raised to 180° (after 15 minutes) the diazepinone immediately changed to a dark red mass. After 45 minutes heating at the same temperature the sample brightened up. The tube was removed from the bath, allowed to cool and the mass was dissolved in benzene (20 ml). The solution was filtered and allowed to stand for 2 hours in water with ice. The yellow crystals which appeared were filtered and dried to give 150 mg of **5** (75%), mp 203-205°. This sample is identical in all respects to the above described compound **5**.

2,3-Dihydro-2-ethoxycarbonylmethyl-2-methyl-4-nitrobenzimidazole **8**.

Method A.

The mixture of 0.9 g (6 mmoles) of 3-nitro-1,2-phenylenediamine **1** and 0.78 g (6 mmoles) of ethyl acetoacetate **2** was kept at 35° temperature for 50 minutes under a stream of argon. Then ethanol (30 ml) and water (100 ml) were added. The obtained precipitate was filtered. Two additional recrystallizations from the same mixture gave 0.51 g of **8** (33%) as dark red crystals, mp 104-105°; R_f 0.90; ir (potassium bromide): ν 3354 and 3280 (NH), 1720 (CO), 1521 and 1338 (NO₂) cm⁻¹; ir (chloroform): ν 3420 (NH), 1720 (CO) cm⁻¹; ¹H nmr (deuteriochloroform): δ 7.32-7.20 (m, 1H, H₅), 7.02 (s, 1H, 3-NH), 6.51-6.40 (m, 2H, H_{6,7}), 4.84 (s, 1H, 1-NH), 4.16 (q, 2H, OCH₂), 2.82 (s, 2H, CH₂CO), 1.67 (s, 3H, CH₃), 1.25 (t, 3H, CH₃).

Anal. Calcd. for C₁₂H₁₅N₃O₄: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.38; H, 5.89; N, 15.95.

Method B.

To a mixture of 5 g (19.5 mmoles) of diamine **1** and 7.75 g (59.5 mmoles) of acetoacetic ester **2** six drops of concentrated

hydrochloric acid were added and carefully mixed. After an additional 3.5 hours at room temperature (18-20°) the reaction mixture became as a slush. Filtration and washing of the precipitate with petroleum ether (40-80°) gave 2.4 g (46%) of crude **8**. Crystallization from aqueous ethanol afforded a pure sample of **8**, mp 104-105°. This sample was identical in all respects to the above described sample.

Preparation of 2-Methyl-4(7)-nitrobenzimidazole **7** from **8**.

A suspension of 0.33 g (1.2 mmoles) of 2,3-dihydro-2-ethoxycarbonylmethyl-2-methyl-4-nitrobenzimidazole **8** in 50 ml of petroleum benzene (80-100°) was refluxed until tlc indicated complete consumption of **8** (about 72 hours). The deposition of a sand-colored precipitate during the refluxing was observed. After cooling to room temperature the precipitate was filtered and washed with 10 ml of ethanol to give 108 mg (87%) of **7**, mp 216-217°, identical to the above described sample.

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