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Investigación

Reaction of 4(7)-Aminobenzimidazole with Ethyl 2-Alkylmalonates in 1,2,4-Trichlorobenzene

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Resumen. La reacción del 4-(7)-aminobencimidazol (**2**) con malonato de etilo o 2-alilmalonato de etilo, utilizando el 1,2,4-triclorobenceno como disolvente, produce benzodiazepin-4,6-dionas y acetamido bencimidazoles. Sin embargo, la reacción de (**2**) con el 2-metilmalonato de etilo, o con derivados de 2-propilo o 2-butilo, produce, además de compuestos similares a los anteriores, un tercer compuesto identificado como una dihidroxiquinolina.

Abstract. The reaction of 4-(7)-aminobenzimidazole (**2**) with ethyl malonate or ethyl 2-allylmalonate, using 1,2,4-trichlorobenzene as the reaction solvent produces benzodiazepin-4,6-diones and acetamidobenzimidazoles. However, reaction of (**2**) with ethyl 2-methylmalonate as well as the 2-butyl and 2-propyl derivatives, produced unknown dihydroxyquinolines in addition to benzodiazepin-4,6-diones and acetamidobenzimidazoles.

Introduction

Since the discovery that 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-1-(1H)-one derivatives, dessigned with the acronym TIBO derivatives, display potent anti-HIV (human immunodeficiency virus, the causative agent of AIDS) activity [2], the synthesis of new 1,4-benzodiazepines has been the subject of intense study in many laboratories. Some of the most interesting novel developments include benzodiazepines (**1**) containing additional substituents in the tricyclic moiety [3]. Recently, as part of our research for new compounds with possible anti-HIV activity, we reported [4] that condensation of 4(7)-aminobenzimidazole (**2**) with ethyl 2-alkylmalonates (**3**) produces 4,5,6,7-tetrahydro-5-alkylimidazo[1,5,4-ef][1,5]benzodiazepine-4,6-diones (**4**), structurally similar to (1), and 2-alkyl-4(7)-(2'-ethoxycarbonyl)acetamidobenzimidazoles (**5a-e**). However, in order to improve the yields of compounds (**4a-e**) (see Table 1), the condensation was carried out using 1,2,4-trichlorobenzene (TCB)[5] as solvent (Fig. 1). We wish to report herein the results of this modification.

Results and Discussion

Refluxing a mixture of 4-(7)-aminobenzimidazole (**2**) and ethyl malonate (**3a**) in 1,2,4-trichlorobenzene gave the benzodiazepinone (**4a**) and the imidazole amide (**5a**) in yields significantly different than those obtained without TCB (54% vs 19% and 6% vs 54%, respectively). On the other hand, reaction of ethyl 2-methylmalonate (**3b**) with (**2**) produced three compounds: a benzodiazepin-4,6-dione (**4b**), an acetamidobenzimidazole (**5b**) and the hitherto unknown dihydroxy-

Table 1. Product Distribution (%) of Reaction of 4(7)-aminobenzimidazole (**2**) with Ethyl 2-alkylmalonates (**3**).

Compound	R	**4** **(*)**	**5** **(*)**	**6** **(*)**
a	H	54 (19)	6 (54)	0 (0)
b	CH_3**	30	23	22
c	C_3H_7	8 (12)	21 (38)	53 (0)
d	C_4H_9	14 (13)	17 (51)	35 (0)
e	C_3H_5	12 (20)	41 (33)	0 (0)

* Yield obtained in previous work [4]

** This substituent was not used in previous work

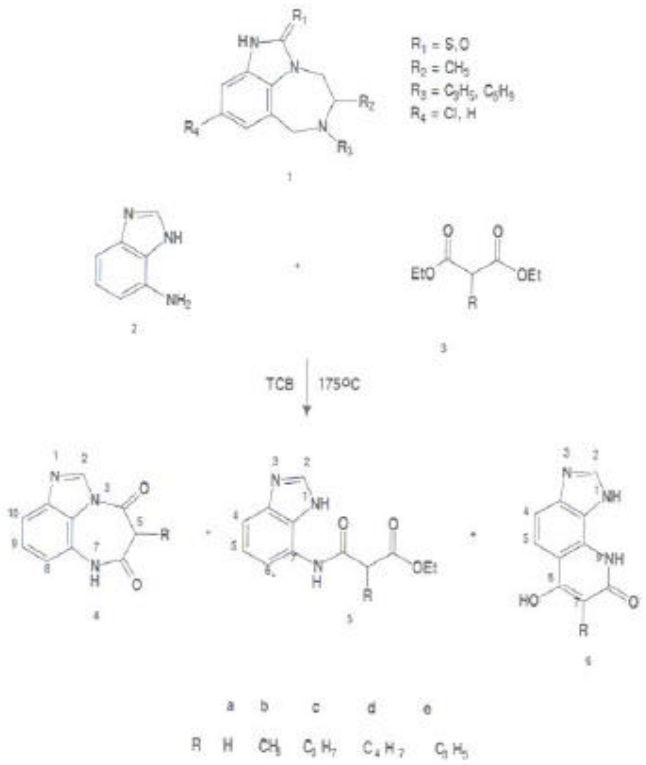

Fig. 1. Products of Reaction of 4(7)-aminobenzimidazole (**2**) with Ethyl 2-alkylmalonates (**3**).

quinoline (**6b**) in 30%, 23% and 22% yield, respectively. The formation of the dihydroxyquinoline **6b** can be rationalized as a malonamide type synthesis [6] from (**5b**) as a possible intermediate, since the aforementionated method uses aniline and malonic ester derivatives as starting materials.

As an extension of these studies we examined the reactions of ethyl 2-propylmalonate (**3c**) and ethyl 2-butylmalonate (**3d**) with (**2**). The reaction of (**2**) with (**3c**) gave (**4c**), (**5c**) and (**6c**) in 8%, 21% and 53% yield, respectively, whereas reaction of (**2**) with **3d** produced (**4d**), (**5d**) and (**6d**) in 14%, 17% and 35% yields. However, reaction of (**2**) with ethyl 2-allylmalonate (**3e**), resulted only in the obtention of benzodiazepin-4,6-dione (**4e**, 12%) and the acetamidobenzimidazole (**5e**, 41%). All structures were fully supported by their spectroscopic data. It is noteworthy that the ^{1}H-NMR spectra of compounds (**6b**) and (**6d**) showed the characteristic signals for both the enol (**6**) and dienol (**6'**) form of these compounds [6] (Fig. 2).

In summary, the reaction of 7(4)-aminobenzimidazole (**2**) with ethyl 2-alkylmalonates, when the alkyl is a methyl, propyl or butyl group, using TCB as the reaction solvent, produces three compounds: benzodiazepin-4, 6-diones, acetamidobenzimidazoles and dihydroxyquinolines. On the other hand, when the 2-alkyl substituent is a hydrogen or an allyl group, the reaction gives benzodiazepin-4,6-diones and acetamidobenzimidazoles as the only products.

Experimental

All melting points are uncorrected. The IR spectra were recorded on a Nicolet FT-55X spectrophotometer. ^{1}H-NMR spectra were determined on a Varian FT-200 and Varian FT-300 instrument, obtained with the pulse sequence included as part of the spectrometer's software; samples were dissolved in hexadeuterio-methyl sulfoxide or deuteriotrifluoroacetic acid solutions tetramethylsilane as the internal standard. Column chromatography was carried out using silica gel 230-400 mesh (Merck

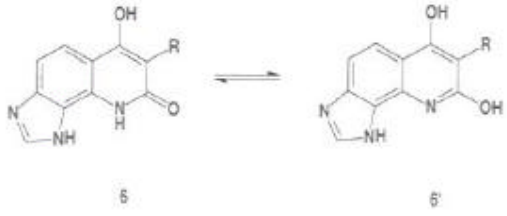

Fig. 2. Enol (**6**) and dienol (**6'**) form of dihydroxyquinolines.

Kieselgel 60 F_{254}). Thin layer chromatography was carried out using silica gel 60, 0.25 mm (Merck Kieselgel 60 PF_{254}). All the solvents used were dried over appropriate drying agent.

The starting 4-(7)-aminobenzimidazole (**2**) was prepared following a reported procedure [7]. The ethyl 2-alkylmalonates (**3a-e**) were purchased from Aldrich. The 4,5,6,7-tetrahydro-5-alkylimidazo[1,5,4-ef][1,5]benzodiazepine-4,6-diones,(**4a,c,d,e**) and 4(7)-(2'-ethoxycarbonyl-2'-alkyl)acetamido benzimidazoles, (**5a,c,d,e**) have been previously prepared [4] and their structures were confirmed by their physical and spectral data.

Reaction of 4-(7)-Aminobenzimidazole **2** with Ethyl malonate **3a**.

A solution of ethyl malonate (**3a**, 288 mg, 1.8 mmoles) in TCB (3.0 ml) was added to 200 mg (1.5 mmoles) of **2** dissolved in hot ethanol. The mixture was stirred at 175°C for 3 h and after this time the solvent was removed in vacuo. The resulting oil was separated by flash chromatography (silica gel, chloroform: ethanol, 70:30) to yield **4a** (162 mg, 54%; mp 280-282°C; lit. 278-279°C [4]) and **5a** (22 mg, 6%; mp 169-171°C; lit. 170-171°C [4]) in pure form.

Reaction of 4-(7)-Aminobenzimidazole **2** with Ethyl 2-methylmalonate **3b**.

Compound **2** (200 mg, 1.5 mmoles) was allowed to react with **3b** (313 mg, 1.8 mmoles) according with the procedure described above to give compounds **4b** (97 mg, 30%), **5b** (90 mg, 23%) and **6b** (78 mg, 22%) in pure form.

4,5,6,7-Tetrahydro-5-methylimidazo[1,5,4-ef][1,5]benzodiazepine-4,6-dione, **4b**.

Mp 249-251°C; IR (KBr) 3291, 1703, 1638 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 10.41 (1H, bs, NH), 8.25 (1H, s, H-2), 7.90 (1H, d, J = 7.8 Hz, H-8), 7.30 (1H, d, J = 7.9 Hz, H-10), 7.15 (1H, dd, J = 7.8, 7.9 Hz, H-9), 4.20 (1H, q, J = 6.9 Hz, H-5), 1.45 (3H, d, J = 6.9 Hz, CH_3-C5). Anal. C, 61.41; H, 4.21, calcd for $C_{11}H_9N_3O_2$, C, 61.39; H, 4.22.

4(7)-(2'-ethoxycarbonyl-2'-methyl)acetamidobenzimidazole, **5b**.

Mp 292-293°C; IR (KBr) 3283, 1736, 1660 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 12.60 (1H, s, NH-3), 10.15 (1H, bs, NH-CO), 8.20 (1H, s, H-2), 7.90 (1H, d, J_o = 7.9 Hz, H-5), 7.27 (1H, d, J_o = 7.8 Hz, H-7), 7.16 (1H, dd, J_o = 7.8, 7.9 Hz, H-6), 4.15 (2H, q, J = 7.2 Hz, OCH_2-CH_3), 4.10 (1H, q, J = 7.0 Hz, H-3'), 1.3 (3H, d, J = 6.9 Hz, CH_3-C3'), 1.15 (3H, t, J = 7.2 Hz, CH_3-CH2O). Anal. C, 59.89; H, 5.41, calcd for $C_{13}H_{14}N_3O_3$, C, 59.99; H, 5.42.

6,8-Dihydroxy-7-methyl-1H-imidazo[4,5-h]quinoline, **6b**.

Mp 239-241°C; IR (KBr) 3246, 1708, 1628 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) **6**: δ 10.80 (bs, 1H, OH), 8.29 (s, H-2), 7.62 (d, J_o = 8.5 Hz, H-5), 7.29 (d, J_o = 8.5 Hz, H-4), 5.30(bs, NH-CO), 1.44 (s, CH_3-C7); **6'**: δ 11.80 (bs, 1H, OH), 8.40 (s, H-2), 7.78 (d, J_o = 8.7 Hz, H-5), 7.34 (d, J_o = 8.7 Hz, H-4), 2.03(3H, s, CH_3-C7). Anal. C, 61.34; H, 4.20, calcd for $C_{11}H_{19}N_3O_2$, C, 61.39; H, 4.22.

Reaction of 4-(7)-Aminobenzimidazole **2** with Ethyl 2-propylmalonate **3c**.

Compound **2** (200 mg, 1.5 mmoles) was allowed to react with **3c** (364 mg, 1.8 mmoles) according with the procedure described above, to produce compounds **4c** (28 mg; 8% mp 184-186°C; lit. [4].

185-186°C), **5c** (89 mg; 21%, oil; lit. [4] oil) and **6c** in (194 mg, 53%).

6,8-Dihydroxy-7-propyl-1H-imidazo[4,5-h]quinoline, **6c**.

Mp 309-311°C; IR (KBr) 3246, 1706, 1626 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) **6'**: δ 11.90 (1H, bs, OH-C6), 10.02 (1H, bs, OH-C8), 8.36 (1H, s, H-2), 7.75 (1H, d, J_o = 8.5 Hz, H-5), 7.28 (1H, d, J_o = 8.5 Hz, H-4), 2.58 (2H, t, J = 7.5 Hz, CH_2-C7), 1.38 (2H, m, CH_2-CH_3), 0.89 (3H, t, J = 7.8 Hz, CH_3-CH_2). Anal. C, 64.24; H, 5.40, calcd for $C_{13}H_{13}N_3O_2$, C, 64.18; H, 5.38.

Reaction of 4-(7)-Aminobenzimidazole **2** with Ethyl 2-butylmalonate **3d**.

Compound **2** (200 mg, 1.5 mmoles) was allowed to react with **3d** (385 mg, 1.8 mmoles), according with the procedure described above, to give compounds **4d** (53 mg; 14%, mp 327-328°C; lit. [4] >300°C), **5d** (72 mg; 17%, oil, lit. [4] oil) and **6d** in (135 mg, 35%).

6,8-Dihydroxy-7-butyl-1H-imidazo[4,5-h]quinoline, **6d**.

Mp 326-328°C; IR (KBr) 3242, 1706, 1624 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) **6**: δ 10.80 (bs, OH), 8.32 (s, H-2), 7.61 (d, J_o = 8.5 Hz, H-5), 7.28 (d, J_o = 8.5 Hz, H-4), 5.30 (bs, NH-CO), 3.30 (m, CH_2-C7), 1.50 (m, CH_2-), 1.23 (m, CH_2-CH_3), 0.76 (t, J = 7.8 Hz, CH_3); **6'**: δ 11.20 (bs, OH), 8.41 (s, H-2), 7.75 (d, J_o = 8.7 Hz, H-5), 7.38 (d, J_o = 8.7 Hz, H-4), 3.30 (m, CH_2-C7), 2.65 (CH_2-), 1.8 (CH_2-CH_3), 0.93 (t, J = 7.8 Hz, CH_3). Anal. C, 65.33; H, 5.85, calcd for $C_{14}H_{15}N_3O_2$, C, 65.35; H, 5.87.

Reaction of 4-(7)-Aminobenzimidazole **2** with Ethyl 2-allylmalonate **3e**.

Compound **2** (200 mg, 1.5 mmoles) was allowed to react with **3e** (360 mg, 1.8 mmoles) according with the procedure described above, to produce compounds **4e** (42 mg; 12%, mp 248-249°C; lit. [4] 240-241°C) and **5e** (176 mg, 41%, oil; lit. [4] oil).

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