Heterocyclic Variants of the 1,5-Benzodiazepine System. VIII. Reaction of 4(7)-Aminobenzimidazole with Ethyl 2-Alkylmalonates

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Reaction of 4(7)-aminobenzimidazole with ethyl 2-alkylmalonates gave the novel 4,5,6,7-tetrahydro-5-alkyl-imidazo[1,5,4-*e,f*][1,5]benzodiazepine-4,6-diones, and the 2-alkyl-4(7)-(2'-ethoxycarbonyl)acetamido-benzimidazoles. The structure of all the products was corroborated by ir, mass spectrometry and ^{1}H-nmr.

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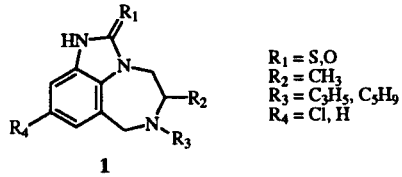
Since the discovery that 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-1(1*H*)-one derivatives, that were assigned the acronym TIBO derivatives, display potent anti-HIV (human immunodeficiency virus, the causative agents of AIDS) activity [3], the 1,4-benzodiazepines have stimulated the exploitation of the chemistry of this class of compounds. Some of the most interesting novel developments are the benzodiazepines containing additional substituents on the tricyclic moiety [4] (Scheme 1). In spite of this, there has been slight interest in the synthesis of 1,5-benzodiazepine analogous [5]; this induces us to report the synthesis of 4,5,6,7-tetrahydro-5-alkylimidazo[1,5,4-*e,f*]-[1,5]-benzodiazepine-4,6-diones, **3a-d**, structural equivalents of **1**, by condensation of 4(7)-aminobenzimidazole **2** with ethyl 2-alkylmalonates (Scheme 2).

Scheme 1

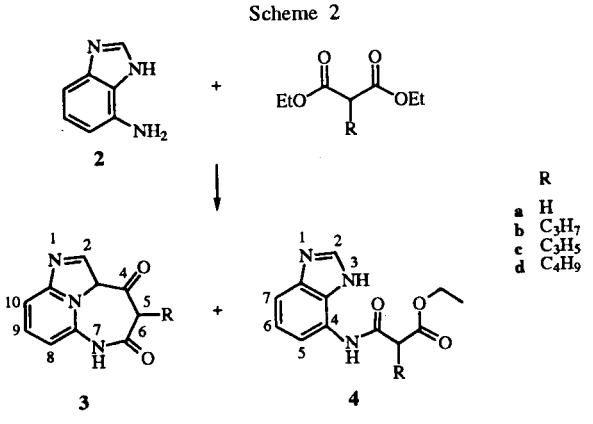


1

Our key intermediate **2** was prepared similarly to literature methods [5]. A mixture of 4(7)-aminobenzimidazole **2** and ethyl 2-alkylmalonates was refluxed to produce **3a-d** and **4a-d** (Scheme 1). Structural assignment of these compounds rest on analytical and spectroscopic evidences.

In the infrared spectra of **3** the appearance of absorption bands at 3320, 3253, 1685 and 1657 was consistent with the presence of amide groups [6]. In the ^{1}H-nmr spectra of derivatives **3** the presence of a one-proton singlet at δ 11.49-9.80, that exchanges with deuterium oxide, confirmed the formation of an secondary amide; a downfield one-proton triplet at δ 3.87-4.19 (in the case of compound **3a** it was a singlet) was assigned to the methine proton attached to C-5. Likewise another one-proton singlet at δ 8.25-8.13 was assigned to the C-2 methine proton. Two doublets at δ 7.90-

Scheme 2



7.96 (J = 7.70 Hz) and δ 7.26-7.31 (J = 7.43 Hz) were assigned to the aromatic protons joined to C-8 and C-10, respectively, whereas a doublet of doublets at δ 7.17-7.16 (J = 7.70 Hz) was assigned to the aromatic proton joined to C-9. Further evidence of the structure of **3** is derived from their mass spectral data. All the compounds showed the molecular ion and their base peak is the m/z 133 ion.

In agreement with the suggested structure the ir spectra (chloroform) of all the compounds **4** exhibited a characteristic band for the ester group at 1744-1770 cm^{-1} together with bands at 3250-3450 and 1648-1670 cm^{-1} asignable to the amide group. Its ^{1}H-nmr spectrum showed a singlet at δ 9.78-9.13 for the -NH proton as well as one singlet for the H-2 proton at δ 8.04-7.98. Two one-proton signals at δ 7.86-7.69 (doublet, J = 7.92 Hz) and δ 7.32 (doublet, J = 7.41 Hz) were assigned to the aromatic protons joined to C-5 and C-7 whereas a doublet of doublets at δ 7.20-7.17 was assigned to the methine proton joined to C-6. It also showed typical signals for the ethyl ester group; one broad quartet (3H, one proton for the 3-NH group) at δ 4.29-4.23 for methylene protons and one triplet at δ 3.90-3.48 for the methyl protons. The triplet at δ 3.70-3.48 was assigned to the proton joined to

C2' (in the case of **4a** compound it was a singlet). The mass spectrum of the compounds showed their molecular ions and its fragmentation is in accordance with to the assigned structure.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Nicolet FT-55X spectrophotometer. The ^1H and ^{13}C-nmr spectra were determined on Varian Gemini 200 and Varian-VXR-300S spectrometers. All nmr spectra were obtained with the pulse sequence as part of the spectrometer's software and was determined in deuteriochloroform, methyl sulfoxide-d_6 and deuteriotrifluoroacetic acid solution containing tetramethylsilane as the internal standard with chemical shifts (δ) expressed downfield from TMS. Mass spectra were obtained with a Jeol SX-100 mass spectrometer.

Compound **2** has been prepared following a reported procedure [5]. The structure of compound **2** was supported by ir, ^1H-nmr and mass spectral data which are similar to those reported.

Reaction of 4(7)-Aminobenzimidazole with Ethyl 2-Alkylmalonates.

General Procedure (R = H).

A mixture of compound **2** (1 g, 7.5 mmoles) and diethyl malonate (2.4 g, 15.0 mmoles) were refluxed with stirring for 1 hour. The oil obtained was then separated by column chromatography (silica gel, chloroform/ethanol, 70/30) into **2a** (0.285 9, 19%) and (chlaroform/ethanol, 95/5) **3a** (1.01 g, 54%).

4,5,6,7-Tetrahydroimidazo[1,5,4-*ef*][1,5]benzodiazepine-4,6-dione, **3a**.

This compound had mp 278-278.5°; ir (potassium bromide): 3320, 3253 (N-H), 1685, 1657 (C=O), 1638 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 10.42 (s, IH, H-7), 8.24 (s, IH, H-2), 7.90 (d, J = 7.70 Hz, IH, H-8), 7.31 (d, J = 7.17 Hz, IH, H-10), 7.33 (dd, J = 7.70 Hz, IH, H-9), 3.87 (s, 2H, H-5); ms: M^+ at m/z 201.

Anal. Calcd. for $C_{10}H_7N_3O_2$: C, 59.69; H, 3.50. Found: C, 59.63; H, 3.48.

4(7)-(2'-Ethoxycarbonyl)acetamidobenzimidazole, **4a**.

This compound had mp 170-171°; ir (neat): 3450 (N-H), 1744 (R-COO-R), 1648 (C=O), 1598 (C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.13 (s, 1H, NH), 7.98 (s, 1H, H-2), 7.86 (d, J = 7.92 Hz, 1H, H-5), 7.32 (d, J = 7.41 Hz, 1H, H-7), 7.17 (dd, J = 7.94 Hz, 1H, H-6), 4.9 (bq, J = 7.6 Hz, 3H, $-OCH_2CH_3$ + NH), 3.9 (s, 2H, H-2'), 1.29 (t, J = 7.6 Hz, 3H, CH_3CH_2O); ms: M^+ at m/z 247.

Anal. Calcd. for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.29. Found: C, 58.25; H, 5.26.

Compound **2** (0.93 g, 7 mmoles) was allowed to react with ethyl 2-propylmalonate (1.41 g, 7 mmoles) according to the procedure described above. It gave compound **3b** in 12% (0.200 g) and **4b** in 38% (0.771 g) yield, respectively.

4,5,6,7-Tetrahydro-5-propylimidazo[1,5,4-*e,f*][1,5]benzodiazepine-4,6-dione, **3b**.

This compound had mp 185-186°; ir (potassium bromide): 3350 (N-H), 1676 (C=O), 1633 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 10.43 (s, 1H, H-7), 8.25 (s, 1H, H-2), 7.92 (d, J = 7.70 Hz, 1H, H-8), 7.29 (d, J = 7.43 Hz, 1H, H-10), 7.16 (dd, J = 7.70 Hz, 1H, H-9), 4.11 (t, J = 6.9 Hz, 1H, H-5), 1.95 (m, 2H, CH_2), 1.38 (m, 2H, CH_2), 0.95 (t, J = 8.45 Hz, 3H, CH_3); ms: M^+ at m/z 243.

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H,5.38; Found.; C, 64.15; H, 5.36.

4(7)-(2'-Ethoxycarbonyl-2'-propyl)acetamidobenzimidazole, **4b**.

This compound was obtained as an oil; ir (neat): 3250 (N-H), 1735 (R-COO-R), 1670 (C=O), 1631 (C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.66 (s, 1H, NH), 8.02 (s, 1H, H-2), 7.69 (d, J = 7.87 Hz, 1H, H-5), 7.45 (d, J = 7.51 Hz, 1H, H-7), 7.20 (dd, J = 7.92 Hz, 1H, H-6), 4.24 (bq, J = 7.33 Hz, 3H, $-OCH_2CH_3$ + NH), 3.49 (t, J = 7.33 Hz, 1H, H-2'), 2.03 (q, J = 7.33 Hz, 2H, CH_2-C2'), 1.45 (m, 2H, CH_2CH_3), 1.29 (t, J = 7.33 Hz, 3H, CH_3CH_2O), 0.94 (t, J = 7.33, 3H, CH_2CH_3); ms: M^+ at m/z 289.

Anal. Calcd. for $C_{15}H_{19}N_3O_3$: C, 62.26; H, 6.61. Found: C, 62.23; H, 6.59.

Compound **2** (0.5 g, 3.8 mmoles) was allowed to react with ethyl 2-allylmalonate (1.52 g, 7.6 mmoles) according to the procedure described above. It gave compound **3c** in 13% (0.118 g) and **4c** in 51% (0.544 g) yield, respectively.

4,5,6,7-Tetrahydro-5-allyl-imidazo[1,5,4-*e,f*][1,5]benzodiazepine-4,6-dione, **3c**.

This compound had mp 240-241°; ir (potassium bromide): 3357 (N-H), 1695 (C=O), 1639 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 10.44 (s, 1H, H-7), 8.13 (s, 1H, H-2), 7.96 (d, J = 7.65 Hz, 1H, H-8), 7.26 (d, J = 7.38 Hz, 1H, H-10), 7.17 (dd, J = 7.70 Hz, 1H, H-9), 5.87 (m, 1H, CH), 5.18 (dd, J_{trans} = 17.1, J_{gem} = 1.79 Hz, 1H, C=CH), 5.03 (dd, J_{cis} = 9.72 Hz, J_{gem} = 1.79 Hz, 1H, C=CH), 4.19 (t, 1H, H-5), 2.75 (t, 2H, CH_2); ms: M^+ at m/z 241.

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.71; H, 4.59. Found: C, 64.69; H, 4.57.

4(7)-(2'-Ethoxycarbonyl-2'-allyl)acetamidobenzimidazole, **4c**.

This compound was obtained as an oil; ir: 3260 (N-H), 1735 (R-COO-R), 1670 (C=O), 1631 (C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.74 (s, 1H, NH), 8.03 (s, 1H), 7.70 (d, J = 7.7 Hz, 1H, H-5), 7.38 (d, J = 7.70 Hz, H-7), 7.20 (dd, J = 7.80 Hz, 1H, H-6), 5.81 (m, J_{trans} = 17.1 Hz, J_{cis} = 10.1 Hz, 1H, $CH{=}CH_2$), 5.15 (dd J_{trans} = 17 Hz, J_{gem} = 1.6 Hz, 1H, $CH_2{=}CH$), 5.09 (dd, J_{cis} = 10.2 Hz, J_{gem} = 1.63 Hz, 1H, $CH_2{=}CH$), 4.24 (bq, J = 7.14 Hz, 3H, OCH_2CH_3 + NH), 3.58 (t, J = 7.18 Hz, H-C2') 2.8 (q, J = 7.11 Hz, 2H, CH_2-C2'), 1.28 (t, J = 7.33 Hz, 3H, CH_3CH_2O); ms: M^+ at m/z 287.

Anal. Calcd. for $C_{15}H_{17}N_3O_3$: C, 62.70; H, 5.96. Found: C, 62.58; H, 5.94.

Compound **2** (0.5 g, 3.8 mmoles) was allowed to react with ethyl 2-butylmalonate (1.64 g, 7.6 mmoles) according to the procedure described above. It gave compound **3d** in 20% (0.193 g) and **4d** in 33% (0.375 g) yield, respectively.

4,5,6,7-Tetrahydro-5-butylimidazo[1,5,4-*e,f*][1,5]benzodiazepine-4,6-dione **3d**.

This compound had mp >300°; ir (potassium bromide): 3239 (N-H), 1670 (C=O), 1615 (C=N) cm^{-1}; ^1H nmr (deuteriofluoroacetic acid): δ 11.50 (s, 1H, H-7), 8.98 (s, 1H, H-2), 7.69 (d, J = 7.70 Hz, 1H, H-8), 7.61 (dd, J = 7.70 Hz, 1H, H-9), 7.46 (d, J = 7.43 Hz,1H, H-10), 4.03 (m, 1H, H-5), 2.20 (m, 2H, CH2-1'), 1.43-0.83 (m, 7H, C_3H_7).

Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.87. Found: C, 65.33; H, 5.84.

4(7)-(2'-Ethoxycarbonyl-2'-butyl)acetamidobenzimidazole, **4d**.

This compound was obtained as an oil; ir: 3283 (N-H), 1736 (R-COO-R), 1668 (C=O), 1630 (C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.78 (s, 1H, NH), 8.04 (s, 1H, H-2), 7.74 (d, J = 7.89 Hz, H-5), 7.37 (d, J = 7.4 Hz, 1H, H-7), 7.20 (dd, J = 7.89 Hz, 1H, H-6), 4.23 (J = 7.24 Hz, 3H, OCH_2CH_3 + NH), 3.48 (t, J = 7.37 Hz, 1H, H-C2'), 2.03 (q, J = 7.11 Hz, 2H, CH_2-C2'), 1.28 (t, J = 7.33 Hz, 3H, CH_3CH_2O), 1.25-1.42 (m, 4H, CH_2CH_2), 0.87 (t, J = 6.84 Hz, 3H, CH_2CH_3); ms: M^+ at m/z 303.

Anal. Calcd. for $C_{16}H_{21}N_3O_3$: C, 63.34; H, 6.97. Found: C, 63.31; H, 6.95

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REFERENCES AND NOTES

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[3] R. Pauwels, K. Andries, J. Desmyter, D. Schols, M. J. Kukla, H. J. Breslin, A. Raeymaeckers, J. Van Gelder, R. Woestenborghs, J. Heykants, K. Schellekens, M. A. C. Janssen, E. De Clercq and P. A. J. Janssen, *Nature*, **343**, 470 (1990).

[4] M. J. Kukla, H. J. Breslin, R. Pauwels, C. L. Fedde, M. Miranda, M. K. Scott, R. G. Sherrill, A. Raeymaeckers, J. Van Gelder, K. Andries, M. A. C. Janssen, E. De Clercq and P. A. J. Janssen, *J. Med. Chem.*, **34**, 746 (1991).

[5] A. Marcos, C. Pedregal and C. Avendaño, *Tetrahedron*, **46**, 7459 (1991).