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Homolytic Substitution and Carbenoidic Reactions in the Preparation of Benzimidazole Derivatives of Pharmaceutical Interest: Synthesis and Properties of (2-Cycloalkyl-1-benzimidazolyl)-*N,N*-diethylacetamides

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The preparation and preliminary biological evaluation of the (2-cycloalkyl-1-benzimidazolyl)-N,N-diethylacetamides **7a–e** are described. Key steps for the preparation of the compounds **7a–d** are (i) the homolytic cycloalkylation of benzimidazole, in which the silver-catalyzed oxidative decarboxylation of the cycloalkanecarboxylic acids **1a–d** by peroxydisulfate is used as a source of alkyl radicals, and (ii) the *N*-alkylation of benzimidazole by the ethoxycarbonylcarbenoid generated by the copper bronze-catalyzed decomposition of ethyl diazoacetate.

Homolytische Substitution und Carbenoid-Reaktionen bei der Herstellung von Benzimidazol-Derivaten von pharmazeutischem Interesse: Synthese und Eigenschaften von (2-Cycloalkyl-1-benzimidazolyl)-N,N-diethylacetamiden

Es werden die Herstellung und die vorläufige biologische Bewertung der (2-Cycloalkyl-1-benzimidazolyl)-N,N-diethylacetamide **7a–e** beschrieben. Die Schlüsselschritte für die Herstellung der Verbindungen **7a–d** bestehen aus einer homolytischen Cycloalkylierung von Benzimidazol, bei der die durch Peroxydisulfat induzierte und durch Silber katalysierte oxydative Decarboxylierung der Cycloalkylcarbonsäuren **1a–d** als Lieferant von Alkylradikalen dient, sowie aus der N-Alkylierung von Benzimidazol. Letztere erfolgt mit einen Ethoxycarbonylcarbenoid, welches durch Kupfer-katalysierte Thermolyse von Ethyldiazoacetat erzeugt wird.

A continuing interest in our laboratory is directed toward the study of chemical and biological properties of imidazole and benzimidazole derivatives[1a–c]. We describe in this paper the synthesis and preliminary biological evaluation of the (1-Benzimidazolyl)-N,N-diethylacetamide derivatives **7a–e**, characterized by a homologous series of substituents (from H to cyclohexyl) at position 2 of the benzimidazole nucleus. We directed our attention, at first, to the synthetic problems connected with the preparation of the 2-cycloalkylbenzimidazoles **3a–d**. A general method for the preparation of 2-substituted benzimidazoles consists in the direct heating of o-phenylenediamine with aliphatic acids[2], with nitriles[3] or with aldehydes[4], and ketones[5].

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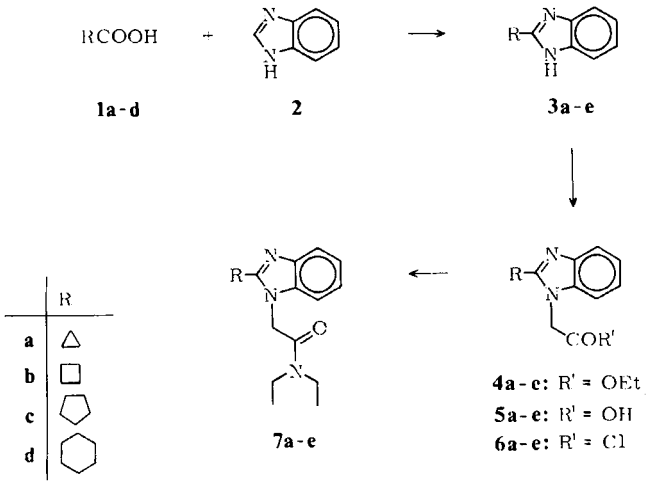
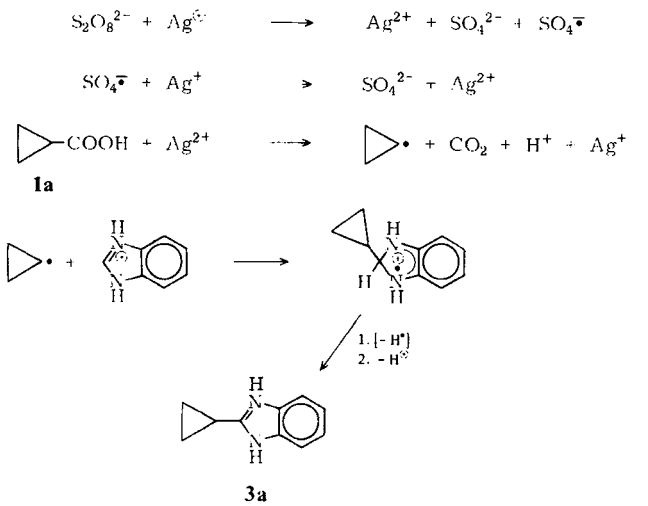
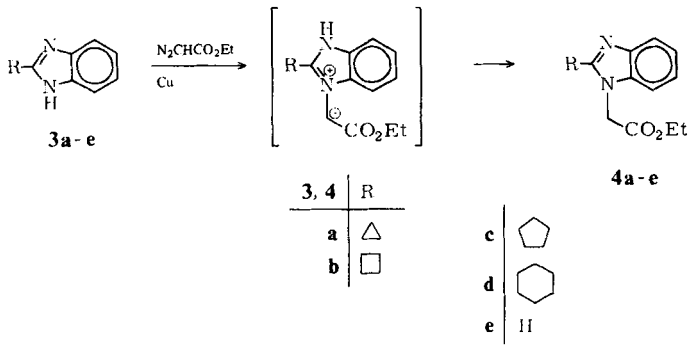


An alternative procedure is based on selective homolytic alkylation reactions recently developed by *Minisci*[6a,b]. We have already reported the application of this method, which allows a large variety of primary, secondary, and tertiary alkyl groups to be introduced into heteroaromatic bases with high selectivity, to the preparation of 2-adamantyl-imidazole and -benzimidazole derivatives[1a]. The same procedure was employed for the preparation of the 2-cycloalkylbenzimidazole derivatives **3a–d**. The reactions were carried out in aqueous solution in the presence of acetonitrile, and the cycloalkyl radicals were generated by silver-catalized decarboxylation of the corresponding acid precursors **1a–d** by ammonium peroxydisulfate, according to the mechanism depicted in Scheme 2 in which the preparation of **3a**, taken as an example, is represented.



In all cases, and in agreement with previous findings[1a,6b], alkylation takes place selectively at position 2 of the benzimidazole nucleus leading to the formation of the 2-cycloalkylbenzimidazoles **3b–d** in fair to good yield. Thus, 2-cyclopentylbenzimidazole **(3c)**, previously prepared[8] in 10 % yield by condensation of **1c** with o-phenylenediamine at 250 °C, is obtained in 60 % yield by the present procedure. This result illustrates the synthetic validity of the method, which is characterized by the ready availability of the starting materials and the ease of carrying out the reactions.

It is known that the electronic configuration of alkyl and cycloalkyl radicals strongly affects their polarity and polarizability and, therefore, their nucleophilicity[7]. The formation of the 2-cyclopropyl derivative **3a** in a lower yield (29 %) can be explained with the high s character, and consequent low nucleophilicity of the cyclopropyl radical intermediate. We have recently reported[1b,c] that alkoxycarbonylcarbenoids generated by the copper bronze-catalyzed decomposition of diazocarbonyl precursors react smoothly with imidazole to give in high yield the corresponding N-alkylated products without concomitant formation of quaternary salts, commonly obtained as by-products in other existing procedures[9,10]. We have utilized this method for the preparation of the ethyl (benzimidazolyl)acetates **4a–e**. Thus, the copper(II) bronze-catalyzed thermolysis of ethyl diazoacetate in the presence of benzimidazole **(3e)** led in good yield to the formation of ethyl (1-benzimidazolyl)acetate **(4e)** and, analogously, the ethyl (2-cycloalkyl-1-benzimidazolyl)acetates **4a–d** were obtained from the corresponding 2-cycloalkylbenzimidazoles **3a–d**. The mechanism of this reaction, which involves an initial attack of the ethoxycarbonylcarbenoid on the tertiary nitrogen of the benzimidazole nucleus, followed by bond rearrangement to the final product, is represented in Scheme 3.



Esters **4a–e**, finally, were converted in two steps into the corresponding *N,N*-diethylacetamido derivatives **7a–e**. Alkaline hydrolysis of **4a–e** led to the corresponding acids **5a–e** which were transformed into the corresponding acyl chlorides **6a–e** by reaction with oxalyl chloride and allowed to react with diethylamine to give the (2-cycloalkyl-1-benzimidazolyl)-N,N-diethylacetamide derivatives **7a–e** in nearly quantitative yield.

Biological Results

The benzimidazolylacetamides **7a–e** were tested on the isolated guinea pig ileum for atropine-like activity in view of previous reports indicating antispasmodic activity for structurally related benzimidazole derivatives[11,12]. All the compounds were found inactive, being unable to antagonize 10^{-7} mol acetylcholine at doses up to 10^{-3} mol. Compounds **7a,b** and **e** were also found inactive in a series of CNS screens, including ^{3}H spiroperidol, ^{3}H-prazosin, ^{3}H-clonidine and ^{3}H-diazepam binding essays[13a–d]. The 2-cyclopentyl- and 2-cyclohexylbenzimidazole derivatives **7c** and **7d** displayed some activity toward ^{3}H-diazepam (0.765 nM) binding, having I_{50} values of $2.5 \cdot 10^{-6}$ M and $4.2 \cdot 10^{-5}$ M, respectively. These results, represented in Fig. 1, indicate that the activity

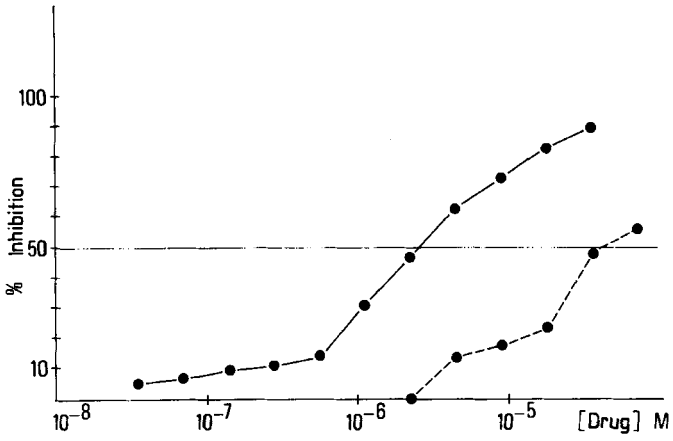


Fig. 1: Inhibition of ^{3}H-Diazepam specific binding by 7c•--•and 7d•—•

shown by **7c** and **7d** is related to the size of the hydrophobic moiety present at C-2 in the benzimidazole nucleus. The preparation of analogues with modified N-1 side chain of the more active compound **7d**, with the aim to increase the activity, is in progress.

The authors are indebted to Dr. *Domenico Barone* (Dow Lepetit) for carrying out part of the biological screenings and to the Ministero della Pubblica Istruzione (Rome, Italy) for financial support.

Experimental

MP: Kofler apparatus, uncorr. *C,H,N-analyses:* automatic analyzer, model 1102, Carlo Erba, Italy. *NMR spectra:* Varian EM 390 spectrometer. *IR spectra:* Beckman Acculab 5 spectrophotometer. *Column chromatography:* Kieselgel 60 (Merck). Ethyl diazoacetate was purchased from Fluka.

Preparation of 2-Cycloalkylbenzimidazole **3a–d**

2-Cyclopropylbenzimidazole **(3a)**: 4.56 g (0.02 mol) ammonium persulfate was added over a 20 min period to a solution of 1.18 g (0.01 mol) benzimidazole, 2.58 g (0.03 mol) cyclopropanecarboxylic acid and 0.34 g (0.002 mol) silver nitrate in 10 ml 2N-H_2SO_4 and 10 ml acetonitrile kept under vigorous stirring at 80 °C. The mixture was stirred at the same temp. for 1 additional h and then poured into an ammonia saturated aqueous solution to give a precipitate (1.2 g) which was washed with ethyl acetate, dried under vac. and chromatographed on a silica gel column. Elution with chloroform yielded 0.45 g (29 %) of pure **3a** with m.p. 234–236 °C (ethyl acetate) lit.[4]: 227–228 °C. – ^{1}H NMR (CD_3OD): δ (ppm) = 0.16–1.16 (m, 4 H, cyclopropyl CH_2), 1.93–2.26 (quint, 1 H, cyclopropyl CH), 6.86–7.43 (m, 4 H, aromatic H). $C_{10}H_{10}N_2$ (158.2) Calc. C 75.9 H 6.37 N 17.7 Found C 75.9 H 6.42 N 17.7.

2-Cyclobutylbenzimidazole **(3b)**: Treatment of 1.18 g, (0.01 mol) benzimidazole with 3.00 g (0.03 mol) cyclobutanecarboxylic acid and 4.56 g (0.02 mol) ammonium persulfate in the presence of 0.34 g (0.02 mol) silver nitrate by the above procedure and chromatography of the residue (1.5 g) on silica gel with chloroform-methanol (97:3) as eluant yielded **3b** (1.1 g, 65 %), m. p. 229–230 °C (ethyl acetate). – ^{1}H NMR (CD_3OD): δ (ppm) = 1.73–2.73 (m, 6 H, cyclobutyl CH_2), 3.5–3.93 (quint, 1 H, cyclobutyl CH), 6.9–7.53 (m, 4 H, aromatic H). $C_{11}H_{12}N_2$ (172.2) Calc. C 76.7 H 7.02 N 16.3 Found C 76.5 H 7.12 N 16.4.

2-Cyclopentylbenzimidazole **(3c)**: Treatment of 4.72 g (0.04 mol) benzimidazole with 13.68 g (0.12 mol) cyclopentanecarboxylic acid and 18.24 g (0.08 mol) ammonium persulfate in the presence of 1.35 g (0.008 mol) silver nitrate by the above procedure yielded a residue (8.5 g) which was chromatographed on a silica gel column. Elution with chloroform yielded 4.40 g (60 %) of **3c**, m.p. 251–253 °C (ethyl acetate). – ^{1}H NMR (CD_3OD): δ (ppm) = 1.66–2.33 (m, 8 H, cyclopentyl CH_2), 3.06–3.6 (quint, 1 H, cyclopentyl CH), 7.03–7.93 (m, 4 H, aromatic H). $C_{12}H_{14}N_2$ (186.3) Calc. C 77.4 H 7.58 N 15.0 Found C 77.1 H 7.43 N 15.3.

2-Cyclohexylbenzimidazole **(3d)**: Treatment of 4.72 g (0.04 mol) benzimidazole with 15.36 g (0.12 mol) cyclohexanecarboxylic acid and 18.24 g (0.08 mol) ammonium persulfate in the presence of 1.35 g (0.008 mol) silver nitrate by the same procedure and chromatography of the residue (9.0 g) on silica gel with chloroform yielded 5.66 g (71 %) of **3d** with m. p. 239–243 °C (ethyl acetate). – ^{1}H NMR (CD_3OD): δ (ppm) = 1.1–2.2 (m, 10 H, cyclohexyl CH_2), 2.6–3.1 (m, 1 H, cyclohexyl CH), 6.9–7.6 (m, 4 H, aromatic H). $C_{13}H_{16}N_2$ (200.3) Calc. C 78,0 H 8.05 N 14,0 Found C 77.8 H 8.09 N 13.5.

Preparation of (1-Benzimidazolyl)acetates **4a–e**

Ethyl (1-benzimidazolyl)acetate **(4e)**: A solution of 1.54 g (13.5 mmol) diethyl diazoacetate in 65 ml of anhydrous xylene is added over a 5h period to a stirred mixture of 1.60 g (13.5 mmol) benzimidazole and 0.5 g copper bronze in 65 ml of anhydrous xylene at 95 °C, and the mixture is stirred at 90 °C for 17 h. The filtrate is evaporated under vac. Chromatography on a silica gel column and elution with chloroform gave 1.17 g (62 %) of **4e** with m.p. 53–64 °C (hexane). – IR ($CHCl_3$): 1730 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.23 (t, 3 H, $CH_2\underline{CH_3}$), 4.19 (q, 2 H, $\underline{CH_2}CH_3$), 4.8 (s, 2 H, CH_2), 7.03–7.90 (m, 5 H, aromatic H). $C_{11}H_{12}N_2O_2$ (204.2) Calc. 64.7 H 5.92 N 13.7 Found C 64.4 H 6.21 N 14.1.

Ethyl (2-cyclopropyl-1-benzimidazolyl)acetate **(4a)**: Treatment of 0.25 g (1.6 mmol) **3a** with 0.18 g (0.16 mmol) ethyl diazoacetate and copper bronze in anhydrous xylene at 110 °C for 18 h as above gave **4a** (0.24 g, 62 %) with m. p. 84–86 °C (hexane). – ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.9–1.23 (m, 4 H, cyclopropyl H), 1.2 (t, 3 H, $CH_2\underline{CH_3}$), 1.66–2.03 (m, 1 H, cyclopropyl 1-H), 4.08 (s, 2 H, CH_2), 4.13 (q, 2 H, $\underline{CH_2}CH_3$), 6.93–7.76 (m, 4 H, aromatic H). $C_{14}H_{16}N_2O_2$ (224.3) Calc. C 68.8 H 6.60 N 11.5 Found C 68.9 H 6.52 N 11.4.

Ethyl (2-cyclobutyl-1-benzimidazolyl)acetate **(4b):** Treatment of 3.00 g (0.02 mol) **3b** with 2.28 g (0.02 mol) ethyl diazoacetate and copper bronze in anhydrous xylene at 110 °C for 24 h as above gave **4b** (3.2 g, 67 %) with m.p. 125–127 °C (hexane). – ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.16 (t, 3 H, $CH_2\underline{CH_3}$), 2.79–1.8 (m, 6 H, cyclobutyl 1-H), 4.06 (q, 2 H, $\underline{CH_2}CH_3$), 4.5 (s, 2 H, CH_2), 6.8–7.56 (m, 4 H, aromatic H). $C_{15}H_{18}N_2O_2$ (258.3) Calc. C 69.7 H 7.02 N 10.8 Found C 69.9 H 7.00 N 10.7.

Ethyl (2-cyclopentyl-1-benzimidazolyl)acetate **(4c):** Treatment of 2.97 g (0.016 mol) **3c** with 1.82 g (0.016 mol) ethyl diazoacetate and copper bronze in anhydrous xylene at 110 °C for 24 h as above gave **4c** (2.79 g, 64 %) with m. p. 94–97 °C (hexane). – ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.23 (t, 3 H, $CH_2\underline{CH_3}$), 1.5–2.23 (m, 8 H, cyclopentyl H), 2.96–3.26 (m, 1 H, cyclopentyl 1-H), 4.16 (q, 2 H, $\underline{CH_2}CH_3$), 4.8 (s, 2 H, CH_2), 7.03–7.8 (aromatic H). $C_{16}H_{20}N_2O_2$ (272.3) Calc. C 70.6 H 7.40 N 10.3 Found C 70.5 H 7.44 N 10.2.

Ethyl (2-cyclohexyl-1-benzimidazolyl)acetate **(4d):** Treatment of 5.00 g (0.025 mol) **3d** with 2.60 g (0.023 mol) ethyl diazoacetate and copper bronze in anhydrous xylene at 110 °C for 24 h as above gave **4d** (4.8 g, 66 %) with m. p. 84–86 °C (hexane). – ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.25 (t, 3 H, $CH_2\underline{CH_3}$), 1.42–2.12 (m, 10 H, cyclohexyl H), 2.4–2.9 (m, 1 H, cyclohexyl 1-H), 4.22 (q, 2 H, $\underline{CH_2}CH_3$), 4.8 (s, 2 H, CH_2), 7.07–7.82 (m, 4 H, aromatic H). $C_{18}H_{22}N_2O_2$ (298.4) Calc. C 72.5 H 7.43 N 9.4 Found C 72.0 H 7.62 N 9.2.

Preparation of (2-Cycloalkyl-1-benzimidazolyl)acetic acids **5a–d**

(2-Cyclopropyl-1-benzimidazolyl)acetic acid **(5a):** A solution of 4 ml 1N-NaOH and 0.4 g **4a** in 4 ml ethanol is heated to reflux for 15 min. The reaction mixture is then evaporated under vac. 5 mol diethyl ether added to the residue and the mixture filtered. The solid residue is dissolved in 5 ml of water and the solution acidified with 2N-HCl. The precipitate thus formed is crystallized from ethanol to give pure **5a** (0.3 g, 85 %) with m. p. 164–166 °C. – ^{1}H NMR ([D_5]pyridine): δ (ppm) = 0.6–1.49 (m, 4 H, cyclopropyl H), 1.98–2.4 (m, 1 H, cyclopropyl 1-H), 5.3 (s, 2 H, $\underline{CH_2}CO_2H$), 6.8–7.4 (m, 4 H, aromatic H), 8.32 (s, 1 H, CO_2H). $C_{12}H_{12}N_2O_2$ (216.2) Calc. C 66.7 H 5.59 N 13,0 Found C 66.4 H 5.70 N 13.1.

(2-Cyclobutyl-1-benzimidazolyl)acetic acid **(5b):** Treatment as above starting from 1.0 g **4b** yielded **5b** (0.7 g, 79 %) with m. p. 254–256 °C (ethanol). – ^{1}H NMR ([D_5]pyridine): δ (ppm) = 1.62–2.72 (m, 6 H, cyclobutyl H), 3.52–4.01 (m, 1 H, cyclobutyl 1-H), 5.02 (s, 2 H, $\underline{CH_2}CO_2H$), 7–7.51 (m, 4 H, aromatic H), 8.51 (s, 1 H, CO_2H). $C_{13}H_{14}N_2O_2$ (230.3) Calc. C 67.8 H 6.13 N 12.2 Found C 67.7 H 6.27 N 12.3.

(2-Cyclopentyl-1-benzimidazolyl)acetic acid **(5c):** Treatment as above starting from 1.0 g **4c** yielded **5c** (0.65 g, 73 %). – ^{1}H NMR (ppm) ([D_5]pyridine): δ (ppm) = 1.16–2.4 (m, 8 H, cyclopentyl H), 3.2–3.53 (m, 1 H, cyclopentyl 1-H), 5.1 (s, 2 H, $\underline{CH_2}CO_2H$), 7–7.51 (m, 4 H, aromatic H), 8.53 (s, 1 H, CO_2H). $C_{14}H_{16}N_2O_2$ (244.3) Calc. C 68.8 H 6.60 N 11.5 Found C 68.8 H 6.68 N 11.5.

(2-Cyclohexyl-1-benzimidazolyl)acetic acid **(5d):** Treatment as above of 0.2 g **4d** yielded **5d** (0.15 g, 83 %) with m. p. 214–219 °C. – ^{1}H NMR ([D_5]pyridine): δ (ppm) = 0.6–1.73 (m, 10 H, cyclohexyl H), 2.33–2.68 (m, 1 H, cyclohexyl 1-H), 4.7 (s, 2 H, $\underline{CH_2}CO_2H$), 6.33–7.06 (m, 4 H, aromatic H), 8.06 (s, 1 H, CO_2H). $C_{15}H_{18}N_2O_2$ (258.3) Calc. C 69.7 H 7.02 N 10.9 Found C 69.7 H 7.22 N 10.9.

Preparation of (2-Cycloalkyl-1-benzimidazolyl)acetamides **7a–e**

(1-Benzimidazolyl)-N,N-diethylacetamide **(7e):** A solution of 1.46 g (1-benzimidazolyl)acetic acid **(5e)** in 8 ml oxalyl chloride was stirred for 5 h at room temp. and the excess oxalyl chloride distilled off at reduced pressure. The residual acyl chloride was dissolved in 10 ml diethylamine and the resulting solution stirred for 2 h at room temp. Evaporation under *vac.*, chromatography of the residue on silica gel and elution with chloroform yielded **7e** (5.5 g, 63 %) with m. p. 118–120 °C (diethyl ether). – ^{1}H NMR ($CDCl_3$): δ (ppm) = 1–1.33 (m, 6 H, ethyl CH_3), 3.18–3.52 (m, 4 H, ethyl CH_2), 4.74 (s, 2 H,

NCH_2CO), 7.03–7.87 (m, 5 H, aromatic H). $C_{13}H_{17}N_3O$ (235.3) Calc. C 66.4 H 7.28 N 20.4 Found C 66.2 H 7.46 N 20.2.

(2-Cyclopropyl-1-benzimidazolyl)-N,N-diethylacetamide **(7a):** Treatment as above starting from 0.25 g **5a** yielded **7a** (0.38 g, 100 %) with m.p. 125–127 °C (diethyl ether). – ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.86–1.3 (m, 10 H, ethyl CH_3 and cyclopropyl H), 1.6–1.96 (m, 1 H, cyclopropyl 1-H), 3.06–3.46 (2 q, 4 H, ethyl CH_2), 4.66 (s, 2 H, $C\underline{H}_2NEt_2$), 6.86–7.56 (m, 4 H, aromatic H). $C_{16}H_{21}N_3O$ (271.4) Calc. C 70.8 H 7.80 N 15.5 Found C 70.8 H 7.83 N 15.4.

(2-Cyclobutyl-1-benzimidazolyl)-N,N-diethylacetamide **(7b):** Treatment as above starting from 0.5 g **5b** yielded **7b** (0.6 g, 97 %) with m.p. 173–175 °C (diethyl ether). – ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.9–1.6 [m, 6 H, $N(CH_2C\underline{H}_3)_2$], 1.76–2.7 (m, 8 H, cyclobutyl H), 3–3.6 [2 q, 4 H, $N(C\underline{H}_2CH_3)_2$], 4.3 (s, 2 H, $C\underline{H}_2NEt_2$), 6.75–7.6 (m, 4 H, aromatic H). $C_{17}H_{23}N_3O$ (285.4) Calc. C 71.5 H 8.12 N 14.7 Found C 71.8 H 8.07 N 14.5.

(2-Cyclopentyl-1-benzimidazolyl)-N,N-diethylacetamide **(7c):** Treatment as above starting from 0.5 g **5c** yielded **7c** (0.52 g, 85 %) with m. p. 129–132 °C (diethyl ether). – ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.7–1.16 [2 t, 6 H, $N(CH_2C\underline{H}_3)_2$], 1.4–2.1 (m, 8 H, cyclopentyl H), 2.63–3.36 [m, 5 H, cyclopentyl 1-H and $N(C\underline{H}_2CH_3)_2$], 4.3 (s, 2 H, $C\underline{H}_2NEt_2$), 6.75–7.6 (m, 4 H, aromatic H). $C_{18}H_{25}N_3O$ (299.4) Calc. C 72.2 H 8.42 N 14.0 Found C 72.5 H 8.30 N 14.0.

(2-Cyclohexyl-1-benzimidazolyl)-N,N-diethylacetamide **(7d):** Treatment as above starting from 0.5 g **5d** yielded **7d** (0.48 g, 78 %) with m.p. 133–135 °C (diethyl ether); – ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.9–1.3 [2 t, 6 H, $N(CH_2C\underline{H}_3)_2$], 1.3–2.06 (m, 10 H, cyclohexyl H), 2.32–2.76 (m, 1 H, cyclohexyl 1-H), 3.06–3.46 [2 q, 4 H, $N(C\underline{H}_2CH_3)_2$], 4.66 (s, 2 H, $C\underline{H}_2NEt_2$), 6.9–7.7 (m, 4 H, aromatic H). $C_{19}H_{27}N_3O$ (313.4) Calc. C 72.8 H 8.68 N 13.4 Found C 72.9 H 8.74 N 13.4.

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