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Preparation of 1-(Aroylalkyl)-1*H*-imidazole and -Benzimidazole Derivatives of Pharmaceutical Interest. A New Synthetic Procedure

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A simple and improved procedure for the preparation of the title compounds is described. It is based on the copper-bronze catalyzed decomposition of aryl diazo ketones in the presence of imidazolic substrates.

Herstellung von 1-(Aroylalkyl)-1*H*-Imidazol- und Benzimidazol-Derivaten von pharmazeutischem Interesse. Ein neues synthetisches Verfahren

Wir beschreiben ein vereinfachtes, verbessertes Verfahren zur Herstellung der Titelverbindungen. Das Verfahren beruht auf der Kupfer-katalysierten Thermolyse von Aryldiazoketonen in Anwesenheit von Imidazolen.

N-Substituted phenethylimidazoles of type **I** have shown to display a variety of pharmacological activities[1]. Among the compounds of this group, miconazole **(1)**[2] is currently used in the treatment of systemic fungal infections, while potent anticonvulsant activity has been demonstrated for a large number of 1-(2-naphthoylmethyl)-1*H*-imidazoles among which **9a** was selected as a particularly promising anticonvulsant agent[3a–c].

The known methods for the preparation of the parent α-arylimidazole-1-ethanol **(Ib)** involve the initial N-alkylation of the imidazole nucleus with 2-halo-methylarylketones in the presence of alkaline reagents[4] followed by the reduction of the imidazole N-aroylalkylderivative thus formed. The crucial N-alkylation step, however, does not proceed satisfactorily due to the recovery of large amounts of the starting imidazole and the formation of relevant amounts of 1,3-bis(phenacyl)imidazolium halides as by-products[4].

We have recently reported that imidazole **(3)**, reacts with diazoesters in presence of copper-bronze as catalyst, to give the corresponding N-carboalkoxymethyl derivatives in high yield[5]. Continued interest in this class of compounds made us turn attention to the applicability of the method to the synthesis of 1-(aroylmethyl)-imidazole derivatives of general structure **Ia**. When diazoacetophenone **(2)** was allowed to react with imidazole **(3)** in the presence of copper-bronze as catalyst, 1-phenacylimidazole **(4)** was obtained as the only reaction product in 76 % yield. Analogously, the reaction of diazoacetophenone with benzimidazole **(5)** yielded 1-phenacyl-benzimidazole **(6a)** in 60 % yield.

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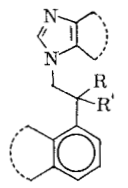
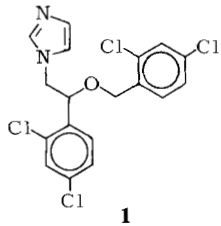


Ia: R = R' = H
b: R = H, R' = OH



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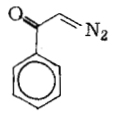

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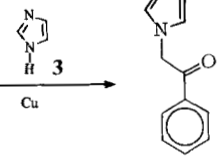

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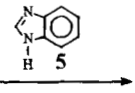

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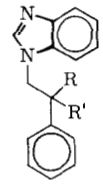
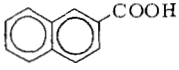


6a: R + R' = O
b: R = H, R' = OH



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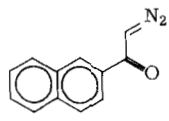

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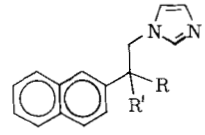

9a: R + R' = O
b: R = H, R' = OH

The reaction was applied, moreover, as a key step in a new synthesis of the anticonvulsant 1-(-2-naphtylmethyl)imidazole derivatives **9a** and **9b**. Successive exposure of 2-naphthoic acid to oxalyl chloride and diazomethane led to the diazo ketone **8**. Decomposition of the diazo compound in a xylene solution of imidazole in the presence of copper-bronze at 85°, produced 1-(-2-naphtoylmethyl)imidazole **(9a)** in 60% yield. α-Arylimidazole-1-ethanol derivatives of general type **Ib** can be easily obtained by sodium borohydride reduction of the corresponding ketoderivatives[6]. By applying this procedure to **9a** and **6a** we have obtained in high yields 1-(-2-hydroxy-2-naphthylethyl)imidazole **(9b)** and 1-(-2-hydroxy-2-phenylethyl)benzimidazole **(6b)**, respectively.

Further exploitations of the methods above described for the preparation of products of pharmaceutical interest is under process in our laboratory.

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Experimental Part

MP: Kofler microscope (uncorr.). *IR Spectra*: Beckmann Acculab 5 spectrophotometer. *^{1}H-NMR Spectra*: Varian EM 390 spectrometer. *Column Chromatography*: Kieselgel 60 (Merck), neutral alumina (Woelm). *Elementary analyses*: automatic analyzer, Model 1102, Carlo Erba (Italy).

1-Phenacyl-imidazole **(4)**

A solution of 1.07 g (7.3 mmol) diazoacetophenone **(2)**[7], and 0.28 g (4 mmol) imidazole **(3)** in 10 ml anhydrous xylene, is added over 5 h to a stirred mixture of 0.28 g (4 mmol) imidazole and 0.06 g copper bronze in 5 ml xylene at 85 °C and the mixture is stirred at 85 °C for 13 h. It is then filtered and the filtrate evaporated under reduced pressure. Chromatography of the residue (1.5 g) on silica gel and elution with chloroform/methanol (49:1) gives 0.9 g of **4**, m.p. 117–118 °C (benzene) (lit.[8] 117–118 °C) (yield 76 %). IR ($CHCl_3$): 1690 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ (ppm) = 5.4 (s, 2H, -$COCH_2$-), 7.1–8.2 (m, 8H, aromatic protons). $C_{11}H_{10}N_2O$ (186.2) Calcd: C 71.0 H 5.41 N 15.1; Found: C 71.0 H 5.38 N 15.0. Finally, further elution with the same solvent gives unreacted, excess imidazole (0.22 g).

1-Phenacylbenzimidazole **(6a)**

A solution of 0.6 g (4 mmol) **2** in 10 ml anhydrous xylene is added over a 5 h period to a stirred mixture of 0.69 g (5 mmol) benzimidazole **(5)** and 0.05 g copper-bronze in 10 ml xylene at 90 °C and the mixture is stirred at 90 °C for 24 h. It is then filtered and the filtrate evaporated under reduced pressure. Chromatography of the residue (1.1 g) on silica gel and elution with chloroform/methanol (49:1) gives 0.58 g **6a**, m.p. 75–80 °C, (yield 60 %). IR ($CHCl_3$): 1690 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ (ppm) = 5.5 (s, 2H_3-$COCH_2$-), 7.1–8.2 (m, 10 H, aromatic protons). $C_{15}H_{12}N_2O$ (236.26). Calcd: C 76.3 H 5.12 N 11.9; Found C 77.0 H 5.01 N 11.7. Finally, further elution with the same solvent gives unreacted excess **5** (0.2 g).

2-Diazoacetylnaphthalene **(8)**[9]

1 g (5.8 mmol) 2-naphthoic acid **(7)** was added to 6 ml freshly distilled oxalyl chloride. The frothing mixture was stirred for 4 h, and then the excess of oxalyl chloride was removed i. vac. dist. A solution of the resulting crystalline acid chloride in 50 ml dry ether was added dropwise during 4 h to an ice-cold, well stirred ethereal solution of 15 mmol diazomethane and 0.585 g (5.8 mmol) triethylamine. The mixture was stirred at 0 °C for additional 4 h and kept at room temp. for 12 h. The mixture was then filtered and the excess of diazomethane was blown off under a stream of nitrogen and the solution concentrated to give 0.650 g of **8**, mp 73–75 °C (light petroleum/ether) (yield 64 %). IR ($CHCl_3$): 2110 (N_2CH), 1620 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ (ppm) = 5.5 (s, 1H, $COCHN_2$) 7–8 (m, 7H, aromatic protons).

1-(2-Naphthoylmethyl)imidazole **(9a)**

A solution of 0.6 g (3 mmol) 1-(diazoacetyl)naphthalene **(8)** in 50 ml anhydrous xylene is added over 5 h period to a stirred mixture of 0.34 g (5 mmol) imidazole **(3)** and 0.6 g copper-bronze in 10 ml xylene

at 85 °C and the mixture is stirred at 85 °C for 16 h. It is then filtered and the filtrate evaporated under reduced pressure. Chromatography of the residue (0.9 g) on neutral alumina (activity IV) and elution with chloroform/methanol (49:1) gives 0.5 g of **9a**, mp 225–227 °C (lit.[3a] 226–228.5 °C) (yield 69 %). IR ($CHCl_3$): 1690 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ (ppm) = 5.4 (s, 2H, $CHCH_2$-), 7.2–8.5 (m, 10 H, aromatic protons). $C_{15}H_{12}N_2O$ (236.26) Calcd: C 76.3 H 5.12 N 11.9; Found C 76.9 H 5.09 N 11.8.

$NaBH_4$ reduction of 1-phenacyl-benzimidazole **(6a)** *to* **6b**

A solution of 31 mg $NaBH_4$ in 5 ml ethanol is added dropwise to a stirred solution of 200 mg **6a** in 10 ml ethanol at 0 °C. Stirring is continued at room temp. for 1 h. Usual work up and chromatography of the residue (200 mg) on silica gel and elution with chloroform/methanol (9:1) gives 170 mg of **6b**, mp 106–108 °C (chloroform/light petroleum) (lit.[10] 106–107 °C) (yield 87 %). ^{1}H-NMR ($CDCl_3$): δ (ppm) = 4.2 (m, 2H, -CH(OH)$\underline{CH_2}$-), 5 (m, 1H, -$\underline{CH}$(OH)-CH_2-); 6.9–7.5 (m, 10 H, aromatic protons). $C_{15}H_{14}N_2O$ (238). Calcd: C 76.3 H 5.12 N 11.9; Found C 76.6 H 5.01 N 11.3.

$NaBH_4$ reduction of 1-(2-naphthoylmethyl)imidazole **(9a)** *to* **9b**

A solution of 66 mg $NaBH_4$ in 10 ml ethanol is added dropwise to a stirred solution of 300 mg **9a** in 20 ml ethanol at 0 °C. Stirring is continued at room temp. for 1 h. Usual work up and chromatography of the residue (280 mg) on silica gel and elution with chloroform/methanol (9:1) gives 260 mg of **9b**, mp 155–158 °C) (lit.[3a] 156–160 °C), (yield 86 %). ^{1}H-NMR ($CDCl_3$): δ (ppm) = 4.3 (m, 2H, -CH(OH)$\underline{CH_2}$-, 5.2 (m, 1H, -$\underline{CH}$(OH)CH_2-), 7.2–7.9 (m, 10 H, aromatic protons). $C_{15}H_{14}N_2O$ (238); Calcd: C 76.3 H 5.12 N 11.9; Found: C 76.4 H 5.1 N 11.6.

References

1 See e.g.: J.A. Katzenellenbogen, R.J. McGorrin, T. Tatee, R.J. Kempton, K.E. Karlson and D.H. Kinder, J. Med. Chem. *24*, 435 (1981) and references therein.

2 a) J. van Cutsen and D. Thienpont, Chemotherapy *17*, 392 (1972); b) P.A.J. Janssen and W. vanBever in Pharmacological and Biochemical Properties of Drug Substances, p. 333, M.E. Goldberg, Ed., publ. Am. Pharm. Ass., Acad. Pharm. Sci., Washington 1979.

3 a) A.M. Walker, M.B. Wallach and D.R. Hirschfeld, J. Med. Chem. *24*, 67 (1981); b) M.B. Wallach, L.R. Hedley, K.E. Peterson and C. Rogers, Fed. Proc. Fed. Am. Soc. Exp. Biol. *39*, 316 (1980); c) D. Nardi, A. Tajana, A. Leonardi, R. Pennini, F. Portioli, M.J. Magistretti and A. Subissi, J. Med. Chem. *24*, 727 (1981) and references therein.

4 J. Brian Jones and D. W. Hysert, Can. J. Chem. *49*, 3012 (1971).

5 R. Pellicciari, M. Curini, N. Spagnoli and P. Ceccherelli, Synthesis *1981*, 629; for related work in the imidazole area see: R. Pellicciari, M.C. Fioretti, P. Cogolli and M. Tiecco, Arzneim. Forsch. *30*, 2103 (1980).

6 E.F. Godefroi, J. Heeres, J. Van Cutsem and P.A.J. Janssen, J. Med. Chem. *12*, 784 (1969).

7 L.T. Scott and M.A. Minton, J. Org. Chem. *42*, 3757 (1977).

8 Beilstein Handbuch der Organischen Chemie, Vol. 48, II, p. 37, Springer-Verlag, Berlin–Göttingen–Heidelberg 1954.

9 For an analogous procedure see: V. Lee and M.S. Newman, Org. Synth., Vol. 50, p. 77.

10 G. Cooper and W. J. Irwin, J. Chem. Soc. Perkin Trans. 1 *1976*, 545.

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