Asian Journal of Chemistry Vol. 15, No. 1 (2003), 519–522

NOTE

Synthesis of Methyl-4-Anilino-3-Amino/Amino-Acetyl Benzoates as Anti-Filarial Agents

M.S.J. BEG†, B.N. SINGH† and PREM RAJ*
Department of Chemistry, Lucknow University, Lucknow, India

A series of methyl-4-anilino-3-amino/amino-acetyl benzoate (**4, 5**) have been synthesized as diethylcarbamizine (DEC) analogs and evaluated against filariasis. Compounds (**4, 5**) show 77.5% and 74.4% microfilaricidal activity respectively at 25 mg/kg for 6 days by I.P. route.

Key Words: Synthesis, Methyl-4-Anilino-3-Amino/Amino-Acetyl Benzoates, Anti-Filarial.

The association of special geometry of diethylcarbamizine (DEC) with its biological activity was first demonstrated by Hewitt *et al.*[1-3]. Further studies on the molecular modifications of DEC revealed the direct relationship of reduced conformational mobility of the compounds with their enhanced anti-filarial activity. A number of such analogs of DEC including centperazine[4-6] have substantiated the above contention. In view of these reports we envisaged the synthesis of a series of 1-(N-substituted-carboxamide-2′-nitrophenyl)-4-methyl piperazines[7], which when evaluated against *L.carinii*, showed very promising results.

The analogs of DEC, the title compounds methyl-4-anilino-3-amino/amino-acetyl benzoates (**4, 5**) were prepared and evaluated for their antifilarial activity.

In order to obtain the title compounds 4-choloro-benzoic acid (**1**) was nitrated and the nitrated product (**2**) was treated with aromatic amines as nucleophiles in a polar solvent to yield 4-anilino-3-nitrobenzoic acid (**3**). Esterification of **3** and subsequent reduction of nitro group furnished 4-anilino-3-aminobenzoic acid methyl esters (**4**). **4** were then transformed into N-acetyl derivatives (**5**). The synthesised compounds have been adequately characterised by spectral data (PMR) and elemental analysis.

Melting points were taken in open capillaries in a sulphuric acid bath and are uncorrected. PMR spectra were recorded on a R-32 Perkin-Elmer (90 MHz) instrument (chemical shifts in δ-scale downfield from TMS internal standard).

†Department of Chemistry, Baldev P.G. College, Baragaon, Varanasi, India.

4-Anilino-3-nitrobenzoic acid: Compound **1** (5 g, 0.032 mol) 4-chloro benzoic acid was dissolved in 20 mL of fuming HNO_3. The contents were refluxed on a water bath for 1 h. The suspension was poured on crushed ice and the moist solid recrystallized from ice-cold methanol to give crystals of 3-nitro-4-chlorobenzoic acid (**2**): yield 68%, m.p. 185°C.

To a solution of 3-nitro-4-chlorobenzoic acid (4 g, 0.019 mol) in 1-propanol (10–12 mL), 8 mL of aniline was added and the mixture refluxed for 12–15 h. The crystals of 4-anilino-3-nitrobenzoic acid (**3**) thus separated were filtered and recrystallized from ethanol: m.p. 257–260°C, yield 65%.

Methyl-4-anilino-3-amino/amino-acetyl benzoate (4)

Compound **3** (5.5 g, 0.021 mole) was dissolved in 2-propanol and 1–2 mL of thionyl chloride was added. The contents were refluxed for 12 h and were cooled. The contents were filtered and recrystallized from ethanol: m.p. 125°C, yield 82%. 4-substituted nitro compound (5.2 g, 0.019 mole) was dissolved in 15 mL methanol. 0.1 g of raney nickel was added. The contents were treated with 1 mL of hydrazine-hydrate and the mixture refluxed for 4 h. The contents were filtered. The product was recrystallised from methanol: yield 60%, m.p. 70°C.

A mixture of **4** (12 g, 0.05 mole), 13 mL of acetic anhydride, 12 mL of glacial acetic acid and 0.1 g of zinc dust was refluxed for 1 h. Crystals were filtered and cooled with ice water. The product then separated was recrystallized from methanol: m.p. 130–135°C, yield 72%.

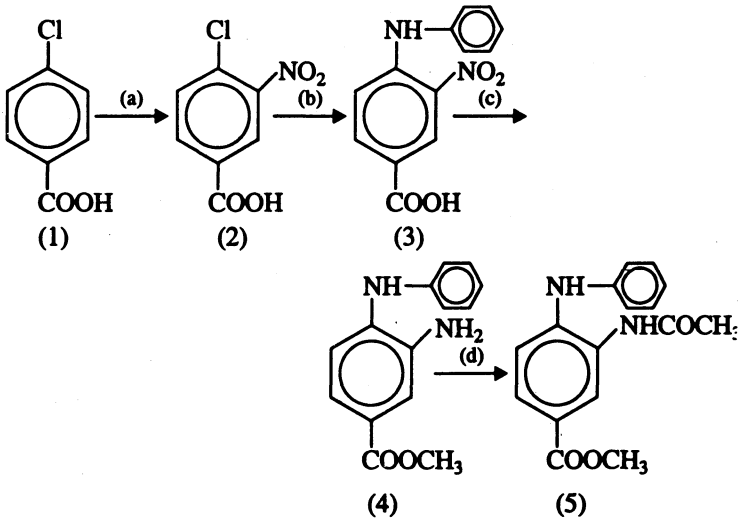
The physical data of compounds **2, 3, 4, 5** are recorded in Table-1.

TABLE-1

Compound No.	Yield (%)	m.p. (°C)	m.f.	% Analysis: Found (Calcd.)	
				C	H
2	68	185	$C_{13}H_{10}N_2O_4$	60.46 (60.50)	3.87 (3.94)
3	65	257	$C_{14}H_{12}N_2O_4$	61.76 (61.92)	4.41 (4.52)
4	60	70	$C_{14}H_{14}N_2O_2$	69.00 (69.40)	5.30 (5.70)
5	72	130	$C_{16}H_{16}N_2O_3$	67.30 (67.60)	5.20 (5.60)

PMR-DATA OF METHYL-4-ANILINO-3 AMINO/AMINO-ACETYL BENZOATES

Compound No.	*PMR δ ($CDCl_3$)*
4.	δ 7.78–7.74 (m, 8H, aromatic proton), 3.7 (s, 3H, $ArCOOCH_3$), 4.5 (s, 2H, Ar—NH_2) and 8.5–9.5 (s, 1H, Ar—NH—Ar)
5.	2.23 (s, 3H, —CH_3) 8.2 (s, 1H, NH—CO), δ 6.76–7.72 (m, 8H, aromatic proton, 3.7 (s, 3H, $ArCOOCH_3$), 4.5 (s, 2H, Ar—NH_2)



Anti-filarial sctivity: After primary toxicity studies carried out in mice, the synthesized compounds were evaluated for anti-filarial screening[9]. Cotton rats *(Sigmodon hispidius)* infected with *L. carinii* used as primary screening models were injected for 6 days intraperitoneally with 25 mg/kg dose of the test compound, a suspension of which was made in 1% T-80 solution in sterile water. 5 mL of blood was taken from the tail of each animal before starting the treatment and thereafter at weekly intervals, *i.e.*, 8th, 15th, 22nd, 29th, 36th and 43rd day. On the 43rd day the treated and control animals were sacrificed to observe the condition of adult parasite.

Compounds **4, 5** exhibited microfilaricidal activity to the extent of 72.5, 54.8 respectively. On 8th day, however, the number of microfilaria increased and crossed the initial count by 22nd day. Compound **5** showed an initial increase in microfilarial counts by 22nd day.

The activity of compound **5**, when compared with DEC, the standard drug in use, showed a better anti-filarial activity. Notwithstanding > 90% microfilaricidal activity of DEC on 8th day, microfilaria reappeared subsequently and also no effect on adult worms was observed. On the other hand, compound **5** showed sustained microfilaricidal action and also exhibited 58.6% macrofilaricidal effects.

ACKNOWLEDGEMENTS

The authors are grateful to the authorities of Lucknow University, Lucknow and Baldev P.G. College, Baragaon, Varanasi for providing facilities. Spectral data and elemental analysis were obtained from RSIC, CDRI Lucknow.

REFERENCES

1. R.I. Hewitt, W.S. Wallace, E. White and Y. Subba Row, *J. Labclin Med.*, **32**, 1923 (1947).
2. R.I. Hewitt, W.S. Wallace, E. White, S.W. Stewart, S. Kushner and Y. Subba Row, *J. Labclin. Med.*, **32**, 1304 (1947).
3. R.I. Hewitt, W.S. Wallace, E. White, S. Kushner, S.W. Stewart and Y. Subba Row, *Ann. NY Acad. Sci.*, **50**, 128 (1948).
4. R. Saxena, R.N. Iyer, N. Anand, R.K. Chatterjee and A.B. Sen, *J. Pharm. Pharmacol.*, **22**, 306 (1970).
5. R. Saxena, S. Sharma, R.N. Iyer and N. Anand, *J. Med. Chem.*, **14**, 1929 (1971).
6. S. Sharma, R.N. Iyer, N. Anand, R.K. Chatterjee, S. Chandra, A. Dutta and A.B. Sen, Indian Pat. (1975) 141941; *Chem. Abstr.*, **92**, 164002 (1980).
7. R.S. Varma, S. Sarin, A. Shukla, N. Fatima and R.K. Chatterjee, *Indian J. Heterocyclic Chem.*, **1**, 17 (1991).
8. J.R. Keneford and J.C.E. Simpson, *J. Chem. Soc.*, 227 (1947).
9. S. Mishra, R.K. Chatterjee and A.B. Sen, *Indian J. Med. Res.*, **73**, 725 (1981).
10. B.M. Khadilkar, V.R. Mestha and S.R. Bhayade, *Indian J. Chem.*, **33B**, 451 (1974).

(*Received*: 6 May 2002; *Accepted*: 28 September 2002) AJC-2877