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NOTE

Synthesis of Acetyl-oxy Phthalimide Derivatives of Diphenyl Amine as Potential Antibacterial

SONAL RAJORA, TAHIRA BANU, DILIP KHATRI and G.L. TALESARA*
Department of Chemistry, College of Science
M.L. Sukhadia University, Udaipur-313 001, India

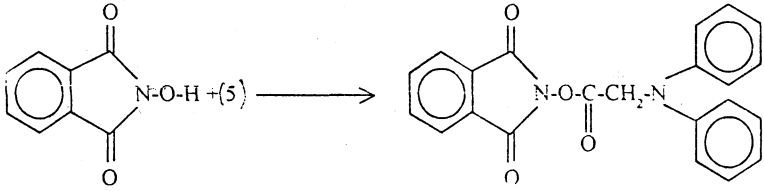
Acetyl-oxy phthalimide derivatives of diphenyl amine are synthesized and screened for their antibacterial activity.

N-substituted diphenyl amine derivatives have been reported to possess diverse pharmacological properties.[1] A large number of phthalimidoxy compounds are also known to have activitis like anti-malarial[2], CNS[3], depressant and anti-hypertensive[4]. In order to synthesize more active pharmacophore, it was thought useful to synthesize some acetyl-oxy phthalimide derivatives of diphenyl amine.

Following reaction sequences have been used to synthesize these compounds:

$$\underset{(1)}{Ph_2NH} + \underset{(2)}{ClCH_2\cdot COOH} \longrightarrow \underset{(3)}{Ph_2NCH_2\cdot COOH}$$

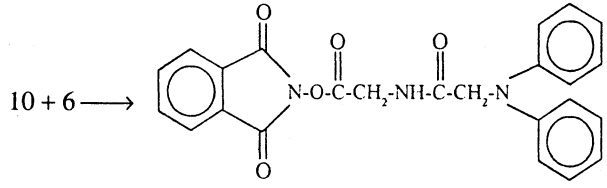
$$\underset{(3)}{} + \underset{(4)}{SOCl_4} \longrightarrow \underset{(5)}{Ph_2NCH_2\cdot COCl}$$



(6) (7)

$$(5) + \underset{(8)}{H_2NCH_2\cdot COOH} \longrightarrow \underset{(9)}{Ph_2NCH_2CONHCH_2\cdot COOH}$$

$$(9) + SOCl_2 \longrightarrow \underset{(10)}{Ph_2NCH_2CONHCH_2\cdot COCl}$$



(11)

Diphenyl amine was treated with α-chloroacetic acid to yield diphenyl amino acetic acid (3). On treating (3) with thionyl chloride corresponding diphenylamino

acetyl chloride (5) was obtained. The reaction of (5) with N-hydroxyphthalimide (6) in dimethyl formamide and in the presence of triethylamine, gave diphenyl amino-N-acetyl-oxy phthalimide (7). Alternatively, (5) was reacted with glycine in alkaline medium to give diphenyl amino-N-acetyl-α-amino ethanoic acid (9). This on reaction with thionyl chloride, followed by N-hydroxy phthalimide gave diphenyl amino-N-acetyl-α-amino ethanoyl-oxy phthalimide (11).

Biological Screening: The synthesized compounds (7 and 11) were screened for their antibacterial activity by paper disc diffusion method[5], using special microbial filter paper disc. These compounds were found active against the test strains of *Salmonella* and *Staph. albus.* Gentamycin and amikacin were used as standard.

All the melting points are uncorrected. Purity of the compounds was tested by TLC and other usual methods.

N-Hydroxyphthalimide (6)

Method of Orndroff and Pratt[6] was used.

Diphenyl aminoacetic acid (3)

Diphenyl amine (0·118 mole, 20 g) in methanol (60 mL) was mixed with α-chloroacetic acid (0·118 mole, 11·5 g) in methanol (30 mL). This was heated on a water bath for 0.5 h. On cooling a solid mass separated which was recrystallized from chloroform (m.p. 43°C) (yield 76%).

Diphenyl aminoacetyl chloride (5)

To a solution of diphenyl aminoacetic acid (0·079 mole, 18·0 g) in chloroform, thionyl chloride (0·158 mole, 18·8 g) was added carefully in fractions. The resultant solution was refluxed on a water bath for 8 h. Excess of thionyl chloride was removed under reduced pressure. On cooling below 5°C, crude product appeared. It was filtered and recrystallized from chloroform (m.p. 159°C) (yield 86%).

Diphenyl aminoacetyl-oxy phthalimide (7)

A solution of diphenyl aminoacetyl chloride (0·05 mole, 12·3 g) and N-hydroxy phthalimide (0·05 mole, 8·2 g) in dimethyl formamide (50 mL) was stirred in presence of triethylamine (0·1 mole, 10·1 g, 14·0 mL) for 14 h. This was filtered and the filtrate was poured into icecold water (500 mL). The crude product was filtered, dried and recrystallized from isopropanol (m.p. 41°C) (yield 53%).

Diphenyl amino-N-acetyl-α-amino ethanoic acid (9)

Glycine (0·122 mole, 1·65 g) was dissolved in cold alkaline methanol (0·122 M NaOH solution, 50 mL). Diphenyl aminoacetyl chloride (0·122 mole, 30·0 g) was added to it and the mixture was stirred for 6 h. The resultant solution was acidified with dilute HCl (25 mL) and extracted with diethyl ether (60 mL). The extract on concentration gave the crude product, which was recrystallized from benzene (m.p. 59°C) (yield 61%).

Diphenyl amino-N-acety-α-amino ethanoyl chloride (10)

The compound (10) was synthesized similarly as in (5) except that (9) was used as starting material. The product was recrystallized from chloroform (m.p. 170°C) (yield 80%).

Diphenyl amino-N-acetyl-α-amino ethanoyl-oxy phthalimide (11)

The compound (11) was synthesized similarly as in (7) expect that (10) was used as starting material. The product was recrystallized from methanol (m.p. 61°C) (yield 45%).

TABLE-I
ELEMENTAL ANALYSIS RESULTS OF SYNTHESIZED COMPOUNDS

Comp. No.	Analytical Data (%)					
	Calculated			Found		
	C	H	N	C	H	N
3	74·00	5·72	6·16	73·81	5·69	6·20
5	68·43	4·88	5·70	68·57	4·80	5·63
7	70·96	4·30	7·52	71·08	4·22	7·43
9	67·60	5·63	9·85	67·51	5·73	10·01
10	63·47	4·95	9·25	63·53	4·79	9·18
11	67·13	4·42	9·79	67·04	4·51	9·75

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