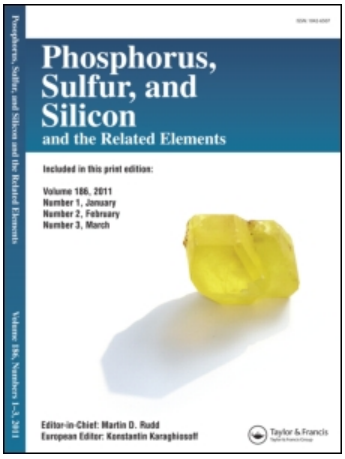

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SYNTHESIS OF SOME NEW *N*[4-(ARYLIDENEAMINO)BENZOYL], *N,N'*-DICYCLOHEXYLUREAS AND 4-THIAZOLIDINONES AND β-LACTAMS THEREFROM

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SYNTHESIS OF SOME NEW *N*[4-(ARYLIDENEAMINO)BENZOYL], *N*,*N*′-DICYCLOHEXYLUREAS AND 4-THIAZOLIDINONES AND β-LACTAMS THEREFROM

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4-Thiazolidinones (**10**) and β-lactams (**12**) of anticipated biological activities were prepared via reaction of *N*[4-(arylideneamino)benzoyl] *N*,*N*′-dicyclohexylureas (**8**) with mercaptoacetic acid and chloroacetyl chloride, respectively. The title compound, *N*(4-aminobenzoyl)-*N*,*N*′-dicyclohexylurea (**4**), was obtained via interaction of 4-aminobenzoic acid (**2**) with dicyclohexylcarbodiimide (**1**). Condensation of (**4**) with aromatic aldehydes afforded the corresponding arylidene derivatives (**8**) in good yield. Biological screening of selected products was done against some strains of bacteria.

Key words: Synthesis; 4-Thiazolidinones; β-Lactams; Urea derivatives.

INTRODUCTION

It was reported that certain amide derivatives are useful as antidepressants,[1] herbicides,[2] and also possess molluscicidal activities.[3] Combination of the parent amide with well known antimicrobial nuclei viz., thiazolidinone[4,5] or azetidinone[6] might intensify the potential biological activity of the derived compounds. Moreover, many urea derivatives were reported to exhibit diverse biological activities as herbicides, fungicides, insecticides and several derivatives showed also antihypertensive activities.[7–10]

RESULTS AND DISCUSSIONS

Synthesis of substituted urea derivatives has a theoretical as well as practical background. For example, the addition of aminobenzoic acids to carbodiimides was considered by many authors such as Zetzsche who suggested carbodiimides as reagents for characterizing carboxylic acids.[11,12]

As reported, carboxylic acids react with carbodiimides to form *N*-acylureas or acid anhydride and the appropriate ureas. The relative yield depends on the nature of the reagent and the conditions.[13] In an attempt to synthesize acylurea derivatives of anticipated biological activities, the starting compound was *N*(4-aminobenzoyl),

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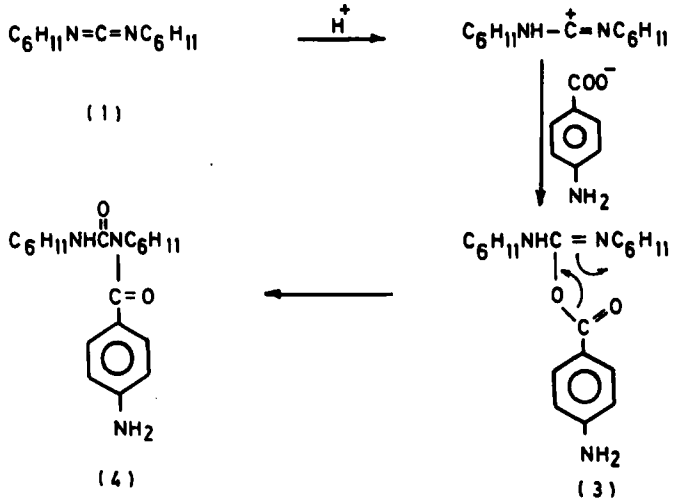
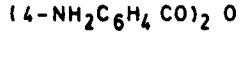
N,*N*′-dicyclohexylurea (**4**), obtained by the reaction of dicyclohexylcarbodiimide (**1**) with 4-aminobenzoic acid (**2**) in ethyl acetate. The expected mechanism for the formation of (**4**) involves protonation of (**1**) followed by attack of the *p*-aminobenzoate anion to form O-(4-aminobenzoyl), *N*,*N*′-dicyclohexylisourea (**3**). The latter rearranges to the stable *N*-acylurea (**4**) through cyclic electron displacement as follows[14]:



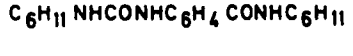
The assigned structure of (**4**) was confirmed by nmr, ms, ir as well as by elemental analysis.

It is worthy to mention that under our reaction conditions, we could not isolate or detect the anhydride (**5**) or the amide (**6**) derived from 4-aminobenzoic acid. Instead, we could isolate a structural isomer of 4 as an ethyl acetate soluble product identified as **7**.[15,16]



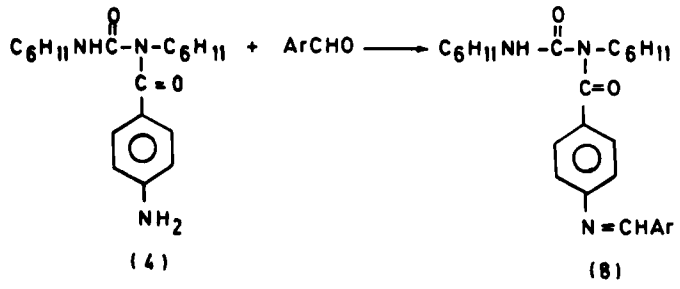
(**5**)

(**6**)



(**7**)

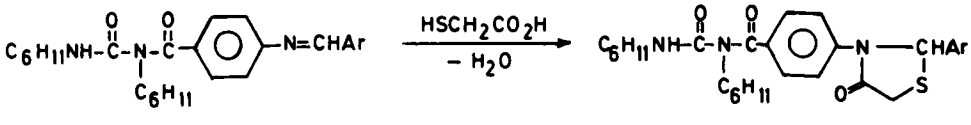
Synthesis of *N*[4-(arylideneamino)]-*N*,*N*′-dicyclohexylurea (**8**) was accomplished via interaction of 4 with aromatic aldehydes in absolute ethanol in the presence of piperidine as a catalyst. The formed Schiff's bases were separated and well characterized using spectroscopic and elemental analyses (Results are presented in Table I). Infrared spectra of 8 showed absorption bands at ~1620 cm^{-1} assignable to $C{=}N_{st}$ and the disappearance of the $-NH_2$ absorption bands.



(4) (8)

Ar	Ar
8: a, C_6H_5	8: g, 4-Br-2-OHC_6H_3
b, 3-$NO_2C_6H_4$	h, 4-NO_2-2-OHC_6H_3
c, 4-$NO_2C_6H_4$	i, 4-$CH_3OC_6H_4$
d, 4-ClC_6H_4	j, $C_6H_5CH=CH$
e, 2-HOC_6H_4	k, $C_{10}H_7$ (α-naphthyl group)
f, 4-Cl-2-OHC_6H_3	l, $C_7H_5O_2$ (piperonyl group)

In continuation of our interest on synthesis of thiazolidinones of anticipated biological activities,[17-19] the arylidene derivatives (**8**) were treated with 2-mercaptoacetic acid in dry benzene (Table II). The reaction mechanism was established by many authors[20] and includes nucleophilic attack on the C=N bond followed by cyclodehydration as follows:



(8) (9)

Ar	Ar
9-a; 3-$NO_2C_6H_4$	9-e; 4-$CH_3OC_6H_4$
b; 4-$NO_2C_6H_4$	f; $C_6H_5CH=CH$
c; 2-OHC_6H_4	g; $C_{10}H_7$ (α-naphthyl group)
d; 4-ClC_6H_4	h; $C_7H_5O_2$ (piperonyl group)

Furthermore, β-lactams received great attention in medicinal chemistry due to the fact that the antibiotic activities of penicillin and cephalosphorin-C is mainly due to the presence of substituted β-lactam ring. Therefore, our investigation involved also the synthesis of azetidinones (**11**) via interaction of (**8**) with chloroacetyl chloride in the presence of triethylamine in dioxane.

The structure of thiazolidinones and β-lactams was confirmed by elemental and

TABLE I

The Analytical Data of Arylidene Derivatives (8)

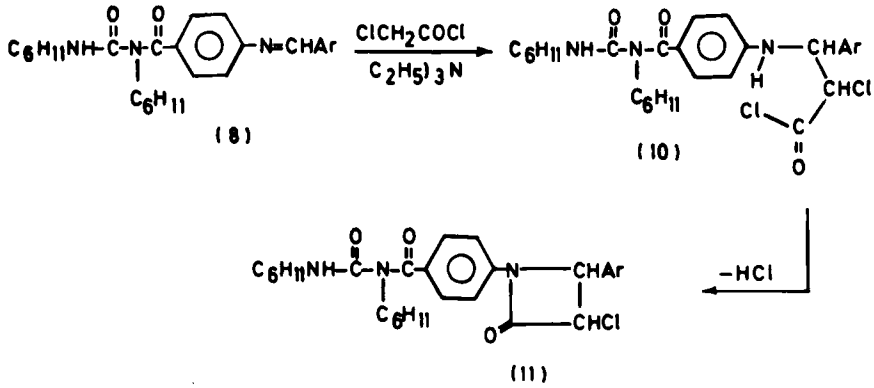
Compd. No.	Yield %	M.P. °C	Mol. Formula	Analysis (Calc./Obs) % C	H	N
8-a	88	228-30	$C_{27}H_{33}N_3O_2$	75.17 75.38	7.65 7.84	9.74 9.89
b	86	208-10	$C_{27}H_{32}N_4O_4$	68.06 68.31	6.72 6.71	11.76 11.95
c	90	281-3	$C_{27}H_{32}N_4O_4$	68.06 68.23	6.72 6.69	11.76 11.78
d	86	297-9	$C_{27}H_{32}N_3O_2Cl$	69.60 69.68	6.87 6.98	9.02 9.13
e	86	305-7	$C_{27}H_{33}N_3O_3$	72.48 72.63	7.38 7.61	9.39 9.48
f	73	303-5	$C_{27}H_{32}N_3O_3Cl$	67.35 67.48	6.64 6.69	8.72 8.91
g	71	310-12	$C_{27}H_{32}N_3O_3Br$	61.59 61.73	6.08 6.17	7.98 7.83
h	76	315-17	$C_{27}H_{32}N_4O_5$	65.85 65.94	6.50 6.61	11.38 11.56
i	77	252-5	$C_{28}H_{35}N_3O_3$	72.88 72.81	7.59 7.78	9.11 9.33
j	80	277-9	$C_{29}H_{35}N_3O_2$	76.14 76.33	7.65 7.81	9.19 9.25
k	76	230-2	$C_{31}H_{35}N_3O_2$	77.33 77.51	7.27 7.41	8.73 8.96
l	61	286-7	$C_{28}H_{33}N_3O_4$	70.73 70.96	6.94 6.79	8.84 8.98

TABLE II

The Analytical Data of 4-thiazolidinones (9)

Compd. No.	Yield %	M.P. °C	Mol. Formula	Analysis (Calc./Obs) % C	H	N	S
9-a	57	160-2	$C_{29}H_{34}N_4O_5S$	63.27 63.41	6.18 6.01	10.18 10.20	5.81 5.93
b	60	170-1	$C_{29}H_{34}N_4O_5S$	63.27 63.41	6.18 6.09	10.18 10.33	5.81 5.70
c	61	250-2	$C_{29}H_{35}N_3O_4S$	66.79 66.70	6.71 6.92	8.06 8.28	6.14 6.33
d	51	252	$C_{29}H_{34}N_3O_4SCl$	62.64 62.69	6.12 6.38	7.56 7.78	5.76 5.82
e	51	206	$C_{30}H_{37}N_3O_4S$	67.28 67.41	6.91 6.70	7.85 7.99	5.98 5.82
f	50	195-6	$C_{31}H_{37}N_3O_3S$	70.00 70.30	6.96 6.75	7.90 7.71	6.02 6.09
g	46	212-13	$C_{33}H_{37}N_3O_3S$	71.35 71.61	6.66 6.69	7.56 7.59	5.76 5.70
h	38	185-7	$C_{30}H_{35}N_3O_5S$	65.57 65.81	6.37 6.12	7.65 7.86	5.82 5.81

spectroscopic analysis. Results are presented in Tables II and III, respectively. I.R. spectra of (**9**) and (**11**) showed absorption bands at 1640–1690 cm^{-1} ($\rangle C{=}O$ of the thiazolidinone) and at 1740–1760 cm^{-1} ($\rangle C{=}O$ of the monocyclic β-lactams), respectively.[21]



(8) (10) (11)

Ar	Ar
11-a, $3\text{-}NO_2C_6H_4$	11-e; $4\text{-}CH_3OC_6H_4$
b, $4\text{-}NO_2C_6H_4$	f; $C_6H_4CH{=}CH$
c, $4\text{-}Br\text{-}2\text{-}HOC_6H_3$	g; $C_{10}H_7$ (α-naphthyl group)
d, $4\text{-}NO_2\text{-}2\text{-}HOC_6H_3$	h; $C_7H_5O_2$ (piperonyl group)

Biological Activities

The antimicrobial activities of some selected compounds (**4–11**) against a variety of Gram-positive and Gram-negative bacteria were determined using the paper disc technique[22] at a concentration 0.1 mg/ml. The bacteria used were: *Bacillus cereus*, *Micrococcus luteus*, *Escherichia coli* and *Pseudomonas aeruginosa*. Data are present in Table IV.

EXPERIMENTAL

All melting points are uncorrected. NMR spectra were obtained using AM 400 Aspect 3000, Bruker (400 MHz) or on a Varian Instrument model (90 MHz). Mass spectra were measured on a Mass spectrometer MAT-311 (Varian) at 70 eV. Ir spectra were displayed on a Pye-Unicam SP 200 G Spectrometer using KBr disc or using IR 4230 Beckman Spectrometer. Elemental analyses (C, H, N) were determined using Ultra microschnell method of Walisch[23] or on Perkin Elmer 240C microanalyzer.

N(4-Aminobenzoyl), N,N'-dicyclohexylurea (**4**): A solution of DCC (2.1 g, 0.01 mole) and 4-aminobenzoic acid (1.4 g, 0.01 mole) in 20 ml dry ethyl acetate, was allowed to stand in the refrigerator over night. The separated crystals (2.1 g, 60% yield) were filtered, washed with ethyl acetate and

TABLE III

The Analytical Data of β-Lactams (11)

Compd. No.	Yield %	M.P. °C	Mol. Formula	Analyses (Calc./Obs.) % C	H	N	Cl
11-a	62	190-1	$C_{29}H_{33}N_4O_5Cl$	62.98	5.97	10.13	6.42
				62.79	5.91	10.28	6.38
b	60	145-6	$C_{29}H_{33}N_4O_5Cl$	62.98	5.97	10.13	6.42
				62.75	5.75	10.35	6.31
c	60	200-1	$C_{29}H_{33}N_3O_4BrCl$	57.75	5.47	6.97	5.89
				57.55	5.36	6.81	5.69
d	67	199	$C_{29}H_{33}N_4O_6Cl$	61.21	5.80	9.85	6.24
				61.41	5.95	9.99	6.38
e	63	212-14	$C_{30}H_{36}N_3O_4Cl$	66.97	6.69	7.81	6.60
				66.75	6.80	7.99	6.80
f	59	209-10	$C_{31}H_{36}N_3O_3Cl$	69.72	6.74	7.87	6.65
				69.91	6.91	7.96	6.79
g	54	230-2	$C_{33}H_{36}N_3O_3Cl$	71.03	6.45	7.53	6.36
				71.31	6.61	7.59	6.41
h	50	213-15	$C_{30}H_{34}N_3O_5Cl$	65.33	6.17	7.62	6.43
				65.51	6.31	7.81	6.31

TABLE IV

Antibacterial activities of some selected compounds

Compd. No.	*Bacillus cer.*	*Microco. luteus*	*Escher. coli*	*Pseudom. aerug.*
4	+	+	—	+
8a	+ + +	—	+ + +	+ + +
8d	+ + +	—	+ + +	+ +
8e	+ + + +	+ +	+ + +	+ + +
8i	+ + +	+ +	+ +	+
9c	+ +	—	+	+ +
9d	+ +	—	+	+ +
9e	+ + +	+	+ +	+
11c	+ +	+	+ +	+ +
11e	+ +	+	+ + +	+ +

Strong effect (+ + + +); medium effect (+ + +); fair effect (+ +); low effect (+), no effect (—).

ethanol. The product was TLC pure and had m.p. 180°C. NMR spectrum revealed signals at δ: 7.45–7.41 (*m*, 2H, the two ortho aromatic protons); 6.64–6.60 (*m*, 2H, the two meta aromatic protons); 5.92 (*d*, 1H, NH); 4.19–4.09 (*m*, 1H, CH.NCO); 3.98 (*S*, 2H, NH_2); 3.56–3.47 (*m*, 1H, $\rangle$CHNHCO); and at 1.08–1.07 (*m*, 20H, CH_2 protons (10 × 2) of the two cyclohexyl rings). I.R. spectrum showed bands at 3470 cm^{-1} for —NH (amide); at 3360 cm^{-1} and 3260 cm^{-1} for —NH_2; at 3060 cm^{-1} for C—H (aromatic); at 2940 cm^{-1} and 2870 cm^{-1} for C—H (aliphatic); and at 1660 cm^{-1} for C=O (amide).

Elemental analysis calculated for $C_{20}H_{29}N_3O_2$: C, 69.97; H, 8.45; N, 12.74% Found: C, 69.55; H, 8.70; N, 12.08%. Mass spectrum showed $[M+1]^+$ peak at m/e 344.

The ethyl acetate solution was evaporated until one fourth its original volume using rotatory evaporator, cooled and the separated precipitate was filtered and titurated with petroleum ether. TLC-in

CH_2Cl_2-Pet. ether (3:1)- showed only one spot. The product was identified as 7,[15,16] m.p. >250°C (decomp.).

Elemental analysis: Calculated for $C_{20}H_{29}O_2N_3$: C, 69.97; H, 8.45, N, 12.24%. Found: C, 69.51; H, 8.04, N, 12.0%. N.M.R. spectrum displayed signals at δ: 7.76 (*s*, 1H, $C_6H_4\underline{N}H\underline{C}O$), 7.76–7.74 (*d*, 1H, $C_6H_{11}\underline{N}H\underline{C}OC_6H_4$-); 7.420–7.439 (*d*, 1H, —NHCO$\underline{N}H\underline{C}_6H_{11}$); 7.28–7.30 (*d*, 2H, two ortho aromatic protons, with respect to carbonyl group); 6.489–6.510 (*d*, 2H, two ortho aromatic protons, with respect to NH group); 4.17–4.18 (*m*, 1H, $\diagdown\underline{C}H$ NHCONH); 3.24–3.27 (*m*, 1H, $\diagdown\underline{C}H$ $\underline{N}H\underline{C}OC_6H_4$-) and 1.01–1.91 (*m*, 20H, CH_2 protons of the two cyclohexyl rings (2 × 10)).

Arylidene Derivatives (**8**): A mixture of equimolecular quantities of 4 (3.4 g, 0.01 mole) and aromatic aldehyde in absolute ethanol (30 ml) in the presence of piperidine (3 drops); was refluxed for three hours. The reaction mixture was concentrated and cooled. The formed precipitate was filtered off and crystallized from ethanol (cf. Table I).

4-Thiazolidinones (**9**): A mixture of 8 (5 mmoles) and mercaptoacetic acid (0.46 g, 5 mmoles) in dry benzene was refluxed using a water separator until the theoretical amount of water has been collected. After most of benzene has been removed under reduced pressure, the residue was dissolved in ether and seeded. In some cases, the thiazolidinone has been separated directly from the benzene solution after cooling (cf. Table II).

2-Azetidinones (**11**): Chloroacetyl chloride (0.02 mol) was added dropwise at room temperature to a well-stirred solution of 8 (0.01 mol) and triethylamine (0.02 mol) in dry dioxane (30 ml). The reaction mixture was stirred for 5 h, left at room temperature for 3 days. The precipitated triethylamine hydrochloride was filtered and washed with dioxan. The combined dioxan solutions were concentrated under vacuum and the residue was collected and crystallized from ethanol-water mixture (cf. Table III).

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