139. Drug-Induced Modifications of the Immune Response

Part 9[1])

4-(Arylamino)-2,5-dihydro-2-oxo-*N*-(*trans*-2-phenylcyclopropyl)furan-3-carboxamides as Novel Antiallergic Compounds

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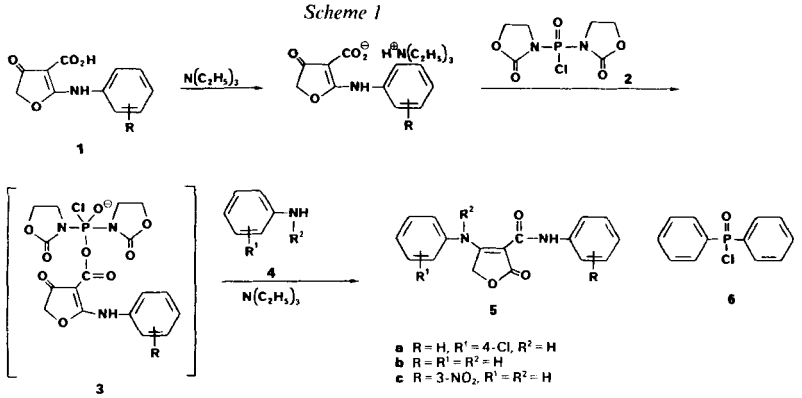
The synthesis and antiallergic activity of a series of 4-(arylamino)-2,5-dihydro-2-oxo-*N*-(*trans*-2-phenylcyclopropyl)furan-3-carboxamides **10** are described. Treatment of *N*-substituted 2-amino-4,5-dihydro-4-oxofuran-3-carboxylic acids **9** with chlorooxobis(2-oxo-1,3-oxazolidin-3-yl)phosphorus (**2**) and an appropriate aromatic amine in the presence of Et_3N, resulted in a novel 3(2*H*)-furanone→2(5*H*)-furanone rearrangement that led to the facile preparation of the new amides **10**. The latter exerted a potent antiallergic activity when tested in the dermal vascular permeability and active anaphylaxis assays in rats. The most active compound **10b** inhibited the action of serotonin, histamine, and bradykinin by 94, 92, and 100%, respectively, when administered intraperitoneally to rats at doses of 100 mg/kg. The present series of **10** represents a novel class of antiallergic agents.

Introduction. – In a recent communication [2], we have reported the synthesis of a number of novel furancarboxamides **5** *via* a novel rearrangement of 2-(arylamino)-4,5-dihydro-4-oxofuran-3-carboxylic acids **1**. The latter when treated with chlorooxobis(2-oxo-1,3-oxazolidin-3-yl)phosphorus (**2**) and a properly substituted aromatic amine **4** in the presence of Et_3N, rearranged to form the corresponding amides **5**, presumably through the intermediacy of the P-containing adduct **3** (*Scheme 1*). It is postulated that the P-atom

Scheme 1



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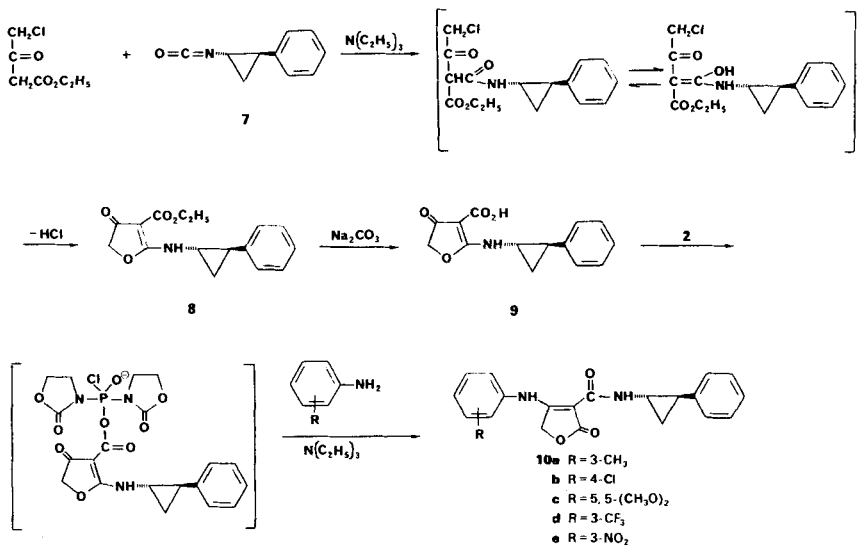
of **2** was initially attacked by the carboxylate anion [3] to produce adduct **3** which will then rearrange (3(2*H*)-furanone→2(5*H*)-furanone) to generate amide **5**[2]).

The 3(2*H*)-furanone→2(5*H*)-furanone rearrangement was also carried out when diphenylphosphinic chloride (**6**) [4–6] was used in place of **2** to activate the carboxyl group of the carboxylic acids **1** [2].

When tested for antiallergic activity in the rat dermal vascular permeability assay, a number of compounds **5** inhibited the effect of mediators on the small blood vessels (see below *Table 1*). As a further extension of our studies, we decided to broaden the scope of the 3(2*H*)-furanone→2(5*H*)-furanone rearrangement by replacing the arylamino group attached to C(5) of **1** with a *trans*-phenylcyclopropylamino moiety (→**9**) and determine whether any change in the nature and/or degree in antiallergic activity of the resulting amides **10** would occur.

Synthesis. – As expected, the cycloaddition of *trans*-2-phenylcyclopropyl isocyanate (**7**) with ethyl 4-chloro-3-oxobutanoate proceeded smootly to give ethyl 4,5-dihydro-4-oxo-2-[(*trans*-2-phenylcyclopropyl)amino]furan-3-carboxylate (**8**) [2] [7–9]. Hydrolysis of the ester group of **8** under mild basic conditions provided the free acid **9**. Reaction of the latter with the P-derivative **2** and an appropriate substituted aniline in the presence of Et_3N resulted in a rearrangement that furnished the amides **10** in yields ranging from 54 to 74% (*Scheme 2*) [2]. The IR and ^{1}H-NMR spectra of compounds **10** are similar to those of amides **5** [2].

Scheme 2



Antiallergic Activity. – As in the case of the *N*-arylamides **5** [1], the antiallergic activity of the *N*-(*trans*-2-phenylcyclopropyl)amides **10** was also evaluated in the rat dermal vascular permeability assay. Compounds **10** were administered intraperitoneally.

[2]) The structure of **5a** was determined by X-ray crystallography, and the experimental details will be reported elsewhere.

Table 1. *Antiallergic Activity of the* N-(trans-*2-Phenylcyclopropyl)amides* **10** *and the* N-*Arylamides* **5** *in the Rat Dermal Vascular Permeability Assay*

Compound	Dose [mg/kg]	Number of rats	Mediator release [% inhibition]		
			serotonin	histamine	brakykinin
5a[a])	100	10	1	3	50[b])
5b[a])	100	10	21[b])	20[b])	63[b])
5c[a])	100	10	0	0	21[b])
10a	100	10	43[b])	72[b])	80[b])
10b	100	10	94[b])	92[b])	100[b])
10c	100	10	62[b])	64[b])	88[b])
10d	100	10	50[b])	63[b])	67[b])
10e	100	10	0	0	0
Cyproheptadine·HCl	1	10	95[b])	94[b])	87[b])

[a]) See [1].
[b]) Statistically significant ($p \leq 0.05$).

As seen from the results in *Table 1*, the antiallergic activity of **10** is significant, especially when compared to that of *N*-arylamides **5**. Thus, at a dose of 100 mg/kg, the 4-(4-chlorophenyl)amino analog **10b** almost completely inhibited the mediator(serotonin, histamine, bradykinin)-induced permeability of the small blood vessels. Furthermore, as observed with derivatives **5**, the overall activity towards the bradykinin action was the most pronounced. When a NO_2 group was introduced into the 4-(arylamino) side chain of compounds **10**, the effect on activity was detrimental; a similar effect was found with the *N*-arylamide analog **5c**.

When tested in the rat active anaphylaxis assay, the most active of amides **5** was the 4-(4-chlorophenyl)amino derivative **5a** [1]. Hence, it was of interest to compare the activity of the latter with that of its 4-(4-chlorophenyl)amino counterpart **10b** in the same assay, especially in view of the significant difference in potency between these two compounds observed in the rat dermal vascular permeability test. As seen from *Table 2*, the antiallergic activity of analog **10b** was nearly twice as potent as that of **5a** and equipotent to that of the standard drug theophylline.

In summary, replacement of the *N*-arylamide group of **5** with the *N*-(*trans*-2-phenylcyclopropyl)amide moiety of **10** markedly increased the activity in the rat dermal vascular permeability assay. The only exception was the 4-(3-nitrophenyl)amino analog

Table 2. *Antiallergic Activity of the 4-(4-Chlorophenyl)amino Derivatives* **5a** *and* **10b** *in the Rat Active Anaphylaxis Assay*

Compound	Dose [mg/kg]	Number of rats	Edema mean values ($\Delta \pm$ S.D.)	% Inhibition
5a[a])	100[b])	19	3.30 ± 2.92	39[c])
10b	100[b])	30	3.33 ± 3.50	70[c])
Theophylline	90[d])	20	3.75 ± 1.77	66[c])

[a]) See [1].
[b]) *Intraperitoneal* administration 1 h prior to challenge.
[c]) Statistically significant ($p \leq 0.05$).
[d]) Oral administration 1 h prior to challenge.

10e which showed a complete lack of activity. Overall, the most promising antiallergic activity was observed with the 4-(4-chlorophenyl)amino compound **10b**.

Based on the above results, the 4-(arylamino)-*N*-(*trans*-2,5-dihydro-2-oxo-2-phenylcyclopropyl)furan-3-carboxamides **10** represent a novel class of antiallergic agents that act most likely through the inhibition of mediator-induced vascular permeability.

Experimental Part

General. M.p.: *Thomas-Hoover* capillary melting point apparatus; uncorrected. IR spectra (KBr): *Nicolet-MX-1-FT* spectrometer. ^{1}H-NMR spectra: *Varian-EM-360-A* (60 MHz) spectrometer; tetramethylsilane as internal standard. All spectra were consistent with the assigned structures.

*2,5-Dihydro-4-[(3-methylphenyl)amino]-2-oxo-*N-(trans-*2'-phenylcyclopropyl)furan-3-carboxamide* (**10a**). Under N_2, Et_3N (2.22 g, 22 mmol) was added dropwise to a soln. of 4,5-dihydro-4-oxo-2-[(*trans*-2-phenylcyclopropyl)amino]furan-3-carboxylic acid (**9**; 2.85 g, 10 mmol) in 22 ml of CH_2Cl_2 at 0° (ice-water bath). Then, *m*-toluidine (1.24 g, 11.57 mmol) was added and the mixture allowed to warm to 10° when **2** (2.80 g, 11.0 mmol) was added in one portion. The mixture was stirred at 10° for 15 min and then at 20° for an additional 2.5 h. H_2O (25 ml) was added and the resulting mixture acidified with 4N HCl (pH 1). The aq. phase was extracted with CH_2Cl_2 and the combined org. phase washed sequentially with H_2O and 5% aq. $NaHCO_3$ soln., dried ($MgSO_4$), and evaporated. The residual solid was recrystallized from EtOH yielding 3.33 g (74%) of **10a**. M.p. 136–137°. IR: 1728 (ring C=O), 1630 (amide), 1619 (arom.). ^{1}H-NMR ($CDCl_3$): 1.12–1.60 (*m*, CH_2(3')); 1.87–2.28 (*m*, H–C(1')); 2.31 (*s*, CH_3); 2.80–3.12 (*m*, H–C(2')); 4.92 (*s*, CH_2(5)); 6.72–7.40 (*m*, 9 arom. H); 7.65–7.95 (*m*, NH); 10.70 (br. *s*, NH). Anal. calc. for $C_{21}H_{20}H_2O_3$: C 72.40, H 5.79, N 8.04; found: C 72.50, H 6.00, N 8.06.

The derivatives **10b–e** were prepared by similar procedures.

*4-[(4-Chlorophenyl)amino]-2,5-dihydro-2-oxo-*N-(trans-*2-phenylcyclopropyl)furan-3-carboxamide* (**10b**). Yield 63%. M.p. 107–109° (EtOH). Anal. calc. for $C_{20}H_{17}ClN_2O_3$: C 65.13, H 4.65, Cl 9.61, N 7.60; found: C 65.21, H 4.76, Cl 9.87, N 7.48.

*4-[(3,5-Dimethoxyphenyl)amino]-2,5-dihydro-2-oxo-*N-(trans-*2-phenylcyclopropyl)furan-3-carboxamide* (**10c**). Yield 50%. M.p. 153–154° (EtOH). Anal. calc. for $C_{22}H_{22}N_2O_5$: C 66.99, H 5.62, N 7.10; found: C 67.12, H 5.72, N 6.84.

*2,5-Dihydro-2-oxo-*N-(trans-*2-phenylcyclopropyl)-4-[(3-(trifluoromethyl)phenyl)amino]furan-3-carboxamide* (**10d**). Yield 54%. M.p. 131–133° (EtOH). Anal. calc. for $C_{21}H_{17}F_3N_2O_3$: C 62.69, H 4.26, F 14.17, N 6.96; found: C 62.80, H 4.28, F 14.23, N 6.86.

*2,5-Dihydro-4-[(3-nitrophenyl)amino]-2-oxo-*N-(trans-*2-phenylcyclopropyl)furan-3-carboxamide* (**10e**). Yield 58%. M.p. 188–190° (AcOEt). Anal. calc. for $C_{20}H_{17}N_3O_5$: C 63.32, H 4.52, N 11.08; found: C 63.42, H 4.56, N 11.02.

Active Anaphylaxis in Rats. Male, *Sprague-Dawley* rats were immunized with a single intraperitoneal injection of 500 µg of a bovine serum albumin (BSA)-alum complex. Fourteen days later, a local anaphylaxis was elicited by a subcutaneous injection (0.1 ml) of 100 µg of BSA in the intraplantar surface of the right hindpaw. Ninety min following this challenge, the paw volume was determined using the mercury plethysmometer. The difference in mean paw volume between the saline and drug-treated groups of animals were compared. The drug at a dose of 100 mg/kg was administered to the rats intraperitoneally 1 h prior to the challenge. Theophylline (100 mg/kg) was the positive reference utilized in the assay. The difference in paw volume of the individual rats per group were averaged to give the value (mean ± standard deviation) at 0 and 90 min. The change in the volume at the 90-min time increment was recorded for each group. The percent of inhibition of edema was calculated as follows: $\{[\Delta$ (control-group volume) – Δ (test-group volume)]/Δ (control-group volume)$\} \cdot 100$ = % inhibition of edema.

Dermal Vascular Permeability Assay in the Rat. Male, *Sprague-Dawley* rats were injected intravenously with 1.0 ml of a 0.5% soln. of *Evan's* blue dye. Ten min later, the animals were intradermally injected (0.1 ml) on the back with 0.1 µg of serotonin, 1.0 µg of bradykinin, and 2.0 µg of histamine. Five min following the injection of the allergic mediators, the rats were sacrificed, the skin reflected, and the mean diameter of each of the blue wheals was

determined. The drugs (100 mg/kg) were administered intraperitoneally 1 h prior to the administration of the dye. The difference in the mean wheal size between the saline and the drug-dosed groups of rats was then determined. Cyproheptadine (1 mg/kg) was included in each assay as a positive reference standard drug. The wheals were measured with vernier calipers. Any measurement under 5 mm in either direction was regarded as no reaction, *i.e.* zero measurement. The mean of each wheal was calculated by multiplying 2 measurements (in two perpendicular directions for each wheal) together and taking the square root of the product.

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