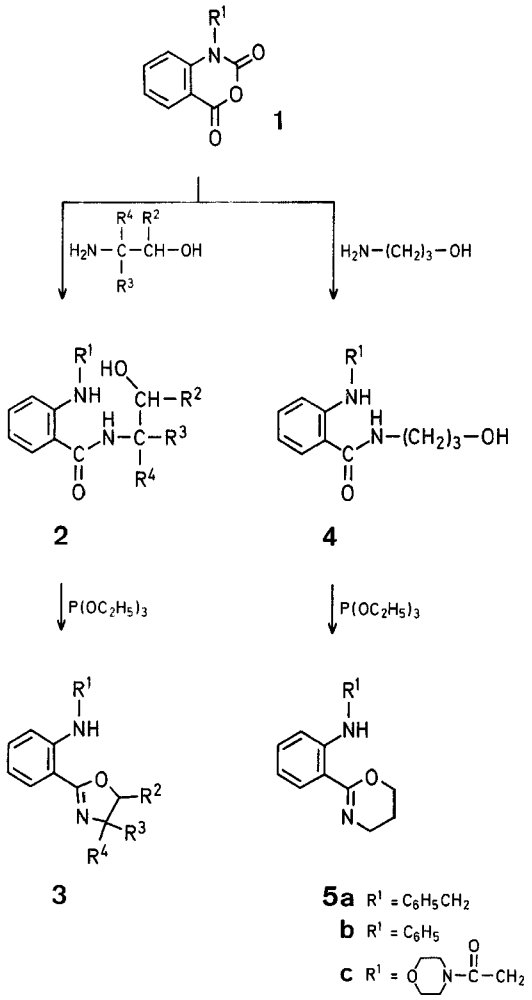
Although these reactions proceed in good yield, they would be unsatisfactory if the starting *N*-(2-hydroxyethyl)-benzamides contained an acid sensitive functionality. In this report we describe an efficient neutral cyclization of 2-substituted amino-*N*-(2-hydroxyalkyl)-benzamides to produce 2-(*o*-substituted-aminophenyl)-4,5-dihydro-1,3-oxazoles **3** and 2-(*o*-substituted-aminophenyl)-5,6-dihydro-4*H*-1,3-oxazines **5** using one equivalent of triethyl phosphite in refluxing xylene as the dehydrating agent.

The required 2-substituted amino-*N*-(2-hydroxyalkyl)-benzamides **2** can be readily produced by treatment of the corresponding *N*-substituted isatoic anhydride[4] **1** with an appropriate amino alcohol using a modification of a previously described procedure[1]. Subsequent cyclization can be effected by the treatment of the substrate with one equivalent of triethyl phosphite in refluxing xylene.



Synthesis of 4,5-Dihydro-1,3-oxazoles and 5,6-Dihydro-4*H*-1,3-oxazines

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In a continuing search for pharmacologically active compounds, we had found it necessary to synthesize 2-(*o*-substituted-phenyl)-4,5-dihydro-1,3-oxazoles. Several literature examples describe the cyclization of *N*-(2-hydroxyethyl)-benzamides with dehydrating agents such as thionyl chloride, sulfuric acid, and *p*-toluenesulfonyl chloride[1,2,3].

To insure that the products are not formed by a simple thermal cyclization, the reaction was performed on **2** ($R^2 = R^3 = R^4 = H$) without the presence of triethyl phosphite and indeed no reaction occurs even when the reaction time was increased by a factor of 5.

Representative products (**3a** and **3d**) exhibit infrared absorption bands at 1637 and 1640 cm^{-1} respectively. The ^1H-N.M.R. spectra of these compounds show a doublet at $\delta = 2.9$ ppm ($NH-CH_3$) which collapses to a singlet on exchange with deuterium oxide. These findings are in complete agreement with those reported in the literature[1].

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Table 1. 2-(Substituted-amino)-*N*-(2-hydroxyalkyl)-benzamides **2** and 2-(Substituted-amino)-*N*-(3-hydroxypropyl)-benzamides **4**

Compound	R^1	R^2	R^3	R^4	Yield [%]	m.p. (solvent)	Molecular formula[a] or Lit. m.p.
2a	H_3C	H	H	H	94	77–80 °C (ether/pentane)	77–80 °C[5]
2b	H_3C	H_3C	H	H	88	71–74 °C (ether/pentane)	$C_{11}H_{16}N_2O_2$ (208.3)
2c	H_3C	H	H_3C	H	35	75–78 °C (pentane)	$C_{11}H_{16}N_2O_2$ (208.3)
2d	H_3C	H	H_3C	H_3C	59	oil	$C_{12}H_{18}N_2O_2$ (222.3)
2e	$C_6H_5-CH_2$	C_2H_5	H	H	70	80–83 °C (pentane)	$C_{18}H_{22}N_2O_2$ (298.4)
2f	H_3C	H	H_3C	$HOCH_2$	51	106–109 °C (ether)	$C_{12}H_{18}N_2O_3$ (238.3)
2g	H_3C	$(C_2H_5)_2N-CH_2$	H	H	73	oil	$C_{15}H_{25}N_3O_2$ (279.4)
4a	$C_6H_5-CH_2$	—	—	—	57	80–83 °C (pentane)	$C_{17}H_{20}N_2O_2$ (284.4)
4b	C_6H_5	—	—	—	78	oil	$C_{16}H_{18}N_2O_2$ (270.3)
4c	morpholino—CO—CH_2	—	—	—	83	164–167 °C (chloroform)	$C_{16}H_{23}N_3O_4$ (321.4)

[a] The microanalysis results were in satisfactory agreement with the calculated values (C ± 0.4%, H ± 0.2%, N ± 0.4%).

Table 2. 2-(*o*-Substituted-phenyl)-4,5-dihydro-1,3-oxazoles **3** and 2-(*o*-Substituted-phenyl)-5,6-dihydro-4*H*-1,3-oxazines **5**

Product	R^1	R^2	R^3	R^4	Yield [%]	m.p. (solvent)	Molecular formula[a] or Lit. m.p.
3a	H_3C	H	H	H	85	62–65 °C (ether)	60–64 °C[1]
3b	H_3C	H_3C	H	H	99	oil	$C_{11}H_{14}N_2O$ (190.2)
3c	H_3C	H	H_3C	H	96	oil	$C_{11}H_{14}N_2O$ (190.2)
3d	H_3C	H	H_3C	H_3C	74	106–109 °C (ether/pentane)	$C_{12}H_{16}N_2O$ (204.3)
3e	$C_6H_5-CH_2$	C_2H_5	H	H	86	oil	$C_{18}H_{20}N_2O$ (280.4)
3f	H_3C	H	H_3C	$HOCH_2$	70	125–128 °C (ether/pentane)	$C_{12}H_{16}N_2O_2$ (220.3)
3g	H_3C	$(C_2H_5)_2N-CH_2$	H	H	65	oil	$C_{15}H_{23}N_3O$ (261.4)
5a	$C_6H_5-CH_2$	—	—	—	35	65–67 °C (pentane)	$C_{17}H_{18}N_2O$ (266.3)
5b	C_6H_5	—	—	—	24	oil	$C_{16}H_{16}N_2O$ (252.3)
5c	morpholino—CO—CH_2	—	—	—	54	113–116 °C (ether)	$C_{16}H_{21}N_3O_3$ (303.4)

[a] The microanalysis results were in satisfactory agreement with the calculated values (C ± 0.4%, H ± 0.3%, N ± 0.4%; exceptions: **5a**, H + 0.5%; **5b**, C + 0.5%).

2-(Substituted-amino)-*N*-(2-hydroxyalkyl)-benzamides 2 and 2-(Substituted-amino)-*N*-(3-hydroxypropyl)-benzamides 4; General Procedure:

A mixture of the substituted isatoic anhydride **1** (0.1 mol) and the appropriate amino alcohol (0.11 mol) in dioxan (400 ml) is stirred at 60 °C for 90 min. The solvent is removed under reduced pressure and the resultant oil is subjected to chromatography on a column of silica gel using 2% methanol/chloroform to elute the product (see Table 1).

2-(*o*-Substituted-phenyl)-4,5-dihydro-1,3-oxazoles 3 and 2-(*o*-Substituted-phenyl)-5,6-dihydro-4*H*-1,3-oxazines 5; General Procedure:

A mixture of the 2-substituted-amino-*N*-(2-hydroxyalkyl)-benzamides **2** or **4** (0.015 mol) and triethyl phosphite (0.016 mol) in xylene (150 ml) is heated under reflux for 24 h. The solvent is removed under reduced pressure and the residue subjected to chromatography on a column of silica gel using chloroform to elute the product (see Table 2).

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