The Synthesis and Ultraviolet Spectra of Some *N*-Aryl-2,3-dihydro-3-oxo-4*H*-1,4-oxazine Derivatives (1)

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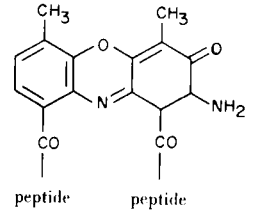
Two new derivatives of the 1,4-oxazine ring system (**3a** and **3b**) derived from *p*-aminobenzamides have been synthesized. The uv absorption spectra of sixteen representative 1,4-oxazines all show two high intensity bands ($\epsilon \sim 10^5$) between 220-400 nm. The positions and intensities of the absorption maxima have been correlated with the steric and electronic effects of the oxazine ring substituents.

Results and Discussion.

The 1,4-oxazines, a class of compounds isosteric with the pyrazines, have demonstrated wide ranging biological activity (3-7). The 1,4-oxazine ring is found in nature in the Actinomycin group of highly active, but toxic, antibiotics (**1**) (8), which show tumor inhibitory properties (9). The fungistat, 2,4-dihydro-7-methoxy 1,4-benzoxazinone (**2**) occurs as a glycoside in corn seedlings (10). The synthesis is reported here of two new derivatives of the 2,3-dihydro-1,4-oxazine ring system (**3a** and **3b**) in which the amino-group of *p*-aminobenzoic acid is incorporated as *N*-4 of the oxazine ring. *p*-Nitrobenzoyl-1-piperidide (**6**), synthesized by refluxing *p*-nitrobenzoyl chloride (**5**) and piperidine (**4**) in anhydrous benzene (11), was reduced to *p*-aminobenzoyl-1-piperidide (**7a**) with stannous chloride and hydrochloric acid according to the method of Wenker (12). *p*-Aminohippuric acid ethyl ester (**7b**) was made in an analogous fashion using the method of Miyatake and Kaga (13). Intermediates **7a** and **7b** possessed satisfactory mass spectral fragmentation patterns and were identical in all respects to authentic samples. Condensation of **7a** and **7b** with 2-bromo-4′-nitroacetophenone (**10**) gave the substituted aminoketones **11a** and



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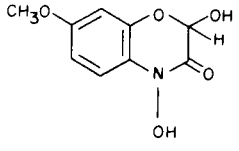

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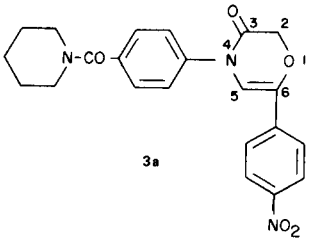
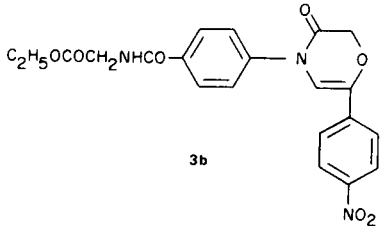
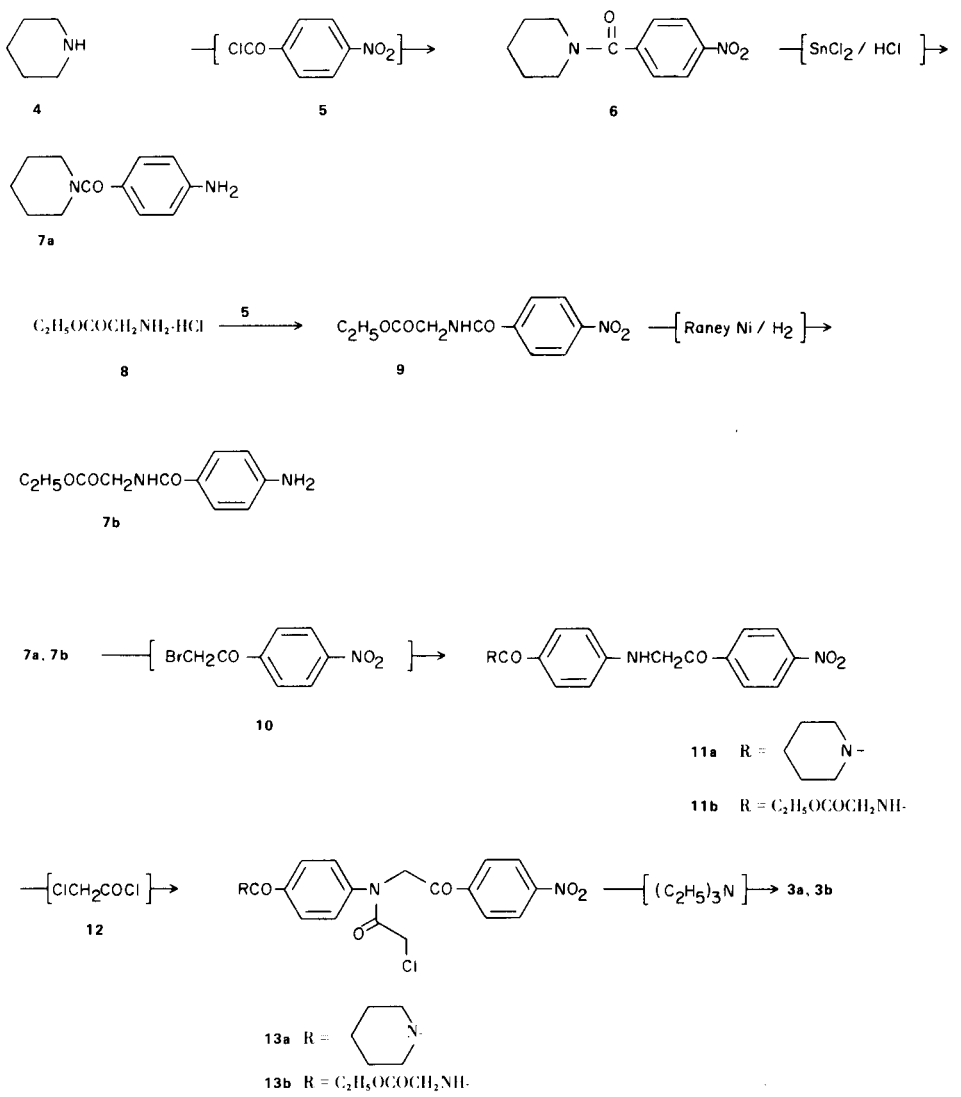


3a



3b



11b respectively. Aminoketone **11b**, for example, showed ir absorption bands at 3430 cm^{-1} and 3360 cm^{-1} (broad) for the N-H stretch vibration. The glycine ester carbonyl absorbed at 1735 cm^{-1} while the aminoketone CO and amide CO groups absorbed at 1689 cm^{-1} and 1635 cm^{-1} respectively. The nmr spectrum (d_6-DMSO/TMS) at 40° supported the assigned structure. A sharp singlet at 8.18 δ (4H) was assigned to the aromatic *p*-nitrophenyl protons. The *p*-ethoxycarbonylmethylaminocarbonylphenyl protons absorbed as a quartet centered at 7.08 δ (4H), with J = 8.5 Hz. The aromatic N-H proton absorbed as a triplet at 7.16 δ (1H), while the aliphatic N-H proton absorbed as a triplet at 6.33 δ (1H). The aminoketone methylene group absorbed as a doublet centered at 4.7 δ (2H), J = 5 Hz. The two remaining methylene groups absorbed as overlapping signals between 4.15 and 3.7 δ (4H). The ester methyl group absorbed as a triplet centered at 1.03 δ (3H) J = 7 Hz.

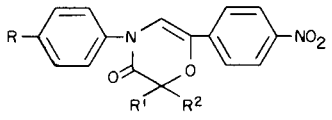
The monochloroacetamides **13a** and **13b** were obtained when their respective precursors **11a** and **11b** were refluxed with an excess of chloroacetyl chloride (**12**) in anhydrous benzene for 6 hours (11). Evaporation of the benzene solution afforded the amides as white crystalline solids in a high state of purity. The infrared spectrum of the amide **13b**, for example, showed the presence of an additional carbonyl group (1685 cm^{-1}) relative to the aminoketone **11b** and an increase in the frequency of the benzoyl amide carbonyl (blue shift from 1635 cm^{-1} to 1665 cm^{-1}). The nmr spectrum supported the assigned structure, with the *p*-nitrophenyl protons absorbing as a quartet centered at 8.13 δ, J = 9 Hz; the *p*-aminobenzoyl protons centered at 7.61 δ, J = 9 Hz; the N-H proton absorbed as a low broad band centered at 6.55 δ; three methylene groups absorbed between 4.16-3.76 δ, integrating to 6H; the ester methyl group absorbed at 1.03 δ as a triplet with J = 7 Hz.

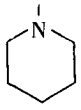
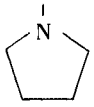
Annelation of chloroacetamides **13a** and **13b** to the 1,4-oxazines **3a** and **3b** respectively was achieved in refluxing benzene/triethylamine mixture. The synthesis was free from isomeric 2-oxoazetidines which in theory could arise by intramolecular *C*-alkylation. Examination of the reaction product prior to purification showed an absence of infrared bands between 1750-1800 cm^{-1} (a diagnostic test for the presence of *beta* lactam carbonyl groups). Furthermore, the characteristic ABX pattern of 4-benzoyl-2-oxoazetidines could not be detected in the nmr spectrum of the unpurified reaction product. This is in keeping with earlier results (1) from which we deduced that this synthesis of 1,4-oxazines while not unequivocal, affords in practice the six-membered ring system, and that control can be established over the course of the intramolecular alkylation by variation of the substituents on the phenacyl ring and/or the variation of *N*-aryl substituents. The infrared spectrum of the oxazine **3a** showed two carbonyl groups (C=O 3-oxo, 1680 cm^{-1}; C=O benzoyl, 1610 cm^{-1}) and distinguished the product from *beta*-lactam. The nmr spectrum showed three ring protons (H_2 (2H) 4.83 δ; H_5 (1H) 7.75 δ) with no evidence of coupling.

Though a number of authors have reviewed the uv absorption spectra of cyclic and acyclic amides (14,15) no data exists concerning the 2,3-dihydro-3-oxo-(4*H*)-1,4-oxazines. Furthermore, we have found, as a result of the present study, that correlations made for substituted acetanilides (15) do not apply for the cyclic amides of the type (**3**). Table I summarizes the uv absorption data for

TABLE I

Ultraviolet Absorption Spectra of Some 1,4-Oxazines (Compounds **3c-3p**, see Ref. 1)



Compound	R	R^1	R^2	λ max (ethanol) nm (ε)		
3a	*p*-(N-CO-)	H	H	366 (12,933)	254 (17,783)	
3b	*p*-($C_2H_5OCOCH_2NHCO$)-	H	H	367 (17,072)	253 (14,702)	222 (16,268)
3c	H	H	H	368 (15,585)	248 (15,035)	
3d	*O*-CH_3	H	H	368 (16,760)	248 (9,896)	
3e	(a)	H	H	364 (16,851)		
3f	H	H	OH	365 (16,182)	248 (13,208)	
3g	H	H	Cl	358 (16,755)	243 (13,539)	
3h	H	H	OMe	363 (17,669)	245 (14,499)	
3i	H	H		373 (10,165)	254 (19,406)	
3j	H	H		371 (10,614)	254 (19,346)	
3k	H	H		366 (12,624)	249 (13,959)	
3l	H	Me	Me	373 (15,664)	253 (14,799)	
3m	*p*-C_2H_5OCO-	H	H	368 (12,879)	269 (17,221)	221 (15,125)
3n	*p*-C_2H_5OCO-	H	OH	363 (15,152)	255 (14,135)	230 (15,457)
3o	*p*-C_2H_5OCO-	H	Cl	358 (18,836)	245 (13,289)	230 (17,366)
3p	*p*-C_2H_5OCO-	H		364 (13,821)	260 (13,503)	232 (14,615)

(a) **3e**: *N*-[α-Naphthyl]-2,3-dihydro-3-oxo-4*H*-6-(*p*-nitrophenyl)-1,4-oxazine.

sixteen representative derivatives of the 3-oxo-1,4-oxazines. In compound **3c** (parent compound for the *N*-phenyl substituted oxazines) there are two high intensity absorptions at λ max (ethanol) 368 nm (ε = 15,570) and at λ max (ethanol) 248 nm (ε = 15,035). *Ortho*-substitution on the *N*-aryl group (*e.g.* **3d**) does not affect the positions of either maxima though it does result in a slight hyperchromic shift (1,200 units of ε) of the 368 nm band. There is, however, a dramatic hypochromic shift (5304 units of ε) in the 248 nm maximum. This hypochromic shift is even more pronounced in the N-(1-naphthyl)-oxazine (**3e**) (16). These results appear to indicate that the intensity of the lower wavelength absorption is a function of the coplanarity of the *N*-aryl substituent, the three valences of nitrogen, and the 3-oxocarbonyl group. Factors which destroy this coplanarity lower the absorption intensity. The effect of small, electronegative substituents on C_2 such as OH, Cl, or OCH_3 (**3f**, **3g**, and **3h** respectively) appears to be a low order blue-shift in the position of the 368 nm maximum. For the 2-chloro oxazine (**3g**) the blue shift is 10 nm. This shift in the position of the maxima is also accompanied by a general hyperchromic shift decreasing in the order of OCH_3, Cl, OH. This hyperchromic shift is paralleled in the 248 nm maxima as well, the overall intensities, however, being generally lower than for **3c**. Since substitution by a 1-piperidyl group caused a red shift in the positions of both maxima (and a strongly hypochromic shift in the higher wavelength maximum accompanied by a corresponding hyperchromic shift in the lower wavelength absorption), we are led to the inference that the effects described are governed both by the steric requirements as well as the electronegativity of the 2-substituents. This conclusion was strengthened by the observation that as the ring size in which the 2-*N* substituent was incorporated was decreased the absorption positions and intensities revert to the values obtained for the 2-hydroxy-oxazine (**3f**) (see Table I). In the 2,2-dimethyloxazine (**3l**) the intensities of the high and low wavelength maxima are relatively unaffected, but there is a red shift of 5 nm in the position of both maxima. In the second class of oxazines that were examined an electron sink was *para*-substituted in the *N*-aryl group. These compounds (**3m**-**3p**) were characterized by three bands between 220-400 nm (*e.g.* **3m**, 368 nm, ε = 12,879; 269 nm, ε = 17,221; 221 nm, ε = 15,125). The generalizations indicated for the *N*-phenyl series of compounds apparently are applicable for the *p*-ethoxycarbonylphenyl substituted oxazines. 2-Substitution, however, has little effect on the intensity of the 220 maximum.

EXPERIMENTAL

1-[4-[*N*-(*p*-Nitrophenacyl)]aminobenzoyl]piperidine (**11a**).

To a stirred solution of 1.4 g. of 4-aminobenzoyl-1-piperidide in a mixture of acetone and ethanol (15 ml. + 1 ml.) was added 0.85 g. of 2-bromo-4′-nitroacetophenone. After stirring at 25° for 24 hours, the yellow precipitate present was filtered, washed with ice-cold 2-propanol and dried to give **11a** in a high state of purity (0.66 g., 55%), yellow needles, m.p. 171-172° (ethanol); ir ν cm^{-1} (potassium bromide): 3410, N-H, 1700, CO ketone, 1620, CO amide; nmr (d_6-DMSO) ppm δ: 8.33 (q, 4H), J = 8 Hz, *p*-nitrophenyl, 7.10 (q, 4H), J = 8 Hz, *p*-aminobenzoyl, 5.23 (t, 1H), N-H, 4.12 (s, broad, 2H), -CH_2-, 3.58 (mc, 4H) piperidine, 1.65 (mc, 6H) piperidine.

Anal. Calcd. for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.66; H, 5.82; N, 11.52.

1-[4-[*N*-(*p*-Nitrophenacyl)-*N*-chloroacetyl]aminobenzoyl]piperidine (**13a**).

To a stirred suspension of 0.5 g. of **11** in 25 ml. of anhydrous benzene (dried over sodium and distilled over potassium permanganate) was added 0.5 g. of freshly distilled chloroacetyl chloride. The mixture was refluxed on an oil bath overnight and the solvent was removed on a rotary evaporator under reduced pressure to give **13a** as a white solid (0.66 g., 100%). Recrystallization from ethanol/cyclohexane gave white needles, m.p. 146-147°; ir ν cm^{-1} (potassium bromide): 1715, CO, ketone, 1680, CO-CH_2Cl, 1620, CO benzamido; nmr (deuteriochloroform): δ 8.23 (q, 4H), J = 8 Hz, *p*-nitrophenyl, 7.50 (s, 4H), *p*-aminobenzoyl, 5.15 (s, 2H), N-CH_2-CO, 4.00 (s, 2H), CO-CH_2-Cl, 3.53 (mc, 4H), piperidine, 1.68 (mc, 6H) piperidine.

Anal. Calcd. for $C_{22}H_{22}ClN_3O_5$: C, 59.53; H, 5.00; N, 9.47. Found: C, 59.13; H, 5.00; N, 9.22.

1-[*p*-[2,3-Dihydro-6-(*p*-nitrophenyl)-3-oxo-4*H*-1,4-oxazin-4-yl]-benzoyl]piperidine (**3a**).

To a stirred suspension of 0.38 g. of **13a** in 10 ml. of benzene was added 3.0 ml. of triethylamine and the mixture was refluxed for 18 hours. The solvent was removed under reduced pressure to give **3a** as an oil which was crystallized by the application of friction under benzene/cyclohexane. The crystals were separated by filtration, washed with water and recrystallized from benzene/cyclohexane to give 0.28 g. (80%) of **3a** as bright yellow needles, m.p. 184-185°; ir ν cm^{-1} (potassium bromide): 1680, 3-oxocarbonyl, 1605, CO-benzoyl amide; nmr (deuteriochloroform) δ: 7.93 (q, 4H), J = 9 Hz, *p*-nitrophenyl, 7.46 (s, 4H), *p*-aminobenzoyl, 6.71 (s, 1H), H_5, 4.78 (s, 2H), H_2, 3.53 (mc, 4H), piperidine, 1.65 (mc, 6H) piperidine.

Anal. Calcd. for $C_{22}H_{21}N_3O_5$: C, 64.86; H, 5.20; N, 10.31. Found: C, 65.10; H, 5.22; N, 10.14.

N-(*p*-Nitrophenacyl)-*p*-aminohippuric Acid Ethyl Ester (**11b**).

A mixture of 9.0 g. of 4-aminohippuric acid ethyl ester and 4.9 g. of 2-bromo-4′-nitroacetophenone in 30 ml. of acetone was stirred at 25° for 6 hours. The deep orange solution containing a yellow precipitate was refrigerated overnight and filtered, the residue was washed with ice-cold 2-propanol, and dried to give 3.7 g. (48%) of **11b** as a yellow crystalline solid. Yellow needles were obtained upon recrystallization from ethanol/ethyl acetate, m.p. 183-184°; ir ν cm^{-1} (potassium bromide) : 3430, 3360,

N-H, 1735, ester CO, 1689, ketone CO, 1635, amide CO; nmr (d_6-DMSO): δ 7.08 (q, 4H) *p*-aminobenzoyl, J = 8.5 Hz, 7.16 (1H), aromatic N-H, 6.33 (1H) aliphatic N-H, 4.70 (d, 2H), aminoketone CH_2, 4.15-3.7 (multiplets, 4H), methylene groups, 1.06 (t, 3H), J = 7 Hz, CH_3.

Anal. Calcd. for $C_{19}H_{19}N_3O_6$: C, 59.21; H, 4.97; N, 10.90. Found: C, 59.39; H, 5.01; N, 11.02.

N-(*p*-Nitrophenacyl)-*N*-chloroacetyl-*p*-aminohippuric Acid Ethyl Ester (**13b**).

A mixture of 0.6 g. of freshly distilled chloroacetyl chloride, 0.6 g. of aminoketone **11b**, and 25 ml. of anhydrous benzene was refluxed for 6 hours. The solvent was removed on a rotary evaporator to give a colorless oil. Refrigeration under 5 ml. of 2-propanol gave 0.93 g. (100%) of the amide **13b** as a white solid which was recrystallized from ethanol/2-propanol to give white needles, m.p. 128-129°; ir ν cm^{-1} (potassium bromide) : 1685, CO, chloroacetamide, 1665, CO, *p*-aminobenzoyl (blue shift of 30 cm^{-1}); nmr (d_6-DMSO): δ 8.13 (q, 4H), J = 9 Hz, *p*-nitrophenyl, 7.61 (q, 4H), J = 9 Hz, *p*-aminobenzoyl, 6.55 (s, 1H), N-H, 4.16-3.76 (m, 6H), methylene groups, 1.03 (t, 3H), J = 7 Hz, CH_3.

Anal. Calcd. for $C_{21}H_{20}N_3O_7Cl$: C, 54.61; H, 4.36; N, 9.10. Found: C, 54.23; H, 4.30; N, 8.96.

Ethyl *p*-[2,3-Dihydro-6-(*p*-nitrophenyl)-3-oxo-4*H*-1,4-oxazin-4-yl]-hippurate (**3b**).

A solution of 0.50 g. of the amide **13b** in 30 ml. of benzene containing 5 ml. of triethylamine was refluxed for 12 hours. Removal of the solvent gave a residue which was triturated with acetone and filtered to give 0.35 g. (74%) of **3b** as a yellow crystalline solid, yellow needles from acetone, m.p. 216-217°; ir ν cm^{-1} (potassium bromide): 1660, CO, amide, 1690, CO, 3-oxo-carbonyl, 1740, CO, ester; nmr (d_6-DMSO): δ 9.00 (t, 1H), N-H, 8.35-7.55 (2 q's, 8H), aromatic protons, 7.75 (s, 1H), H_5, 4.83 (s, 2H), H_2, 4.20 (d, 2H), J = 7 Hz, aminomethylene CH_2, 4.13 (q, 2H), J = 7 Hz, ester CH_2, 1.2 (t, 3H), J = 7 Hz, ester CH_3.

Anal. Calcd. for $C_{21}H_{19}N_3O_7$: C, 59.29; H, 4.50; N, 9.88. Found: C, 58.92; H, 4.49; N, 9.73.

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