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Substituted 3-Phenyl-1,3-benzoxazine-2,4-diones and their Bacteriostatic Activity

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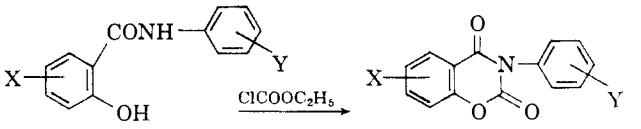
The antibacterial activity of various halo- and nitrosalicylanilides is well known.[1] Many of these compounds demonstrate good bacteriostatic activity and are substantive to skin and cotton cloth. We wish to report the preparation and antibacterial properties of some substituted 3-phenyl-1,3-benzoxazine-2,4-diones, which are heterocyclic derivatives of salicylanilides.

Only two compounds of this type have been reported in the literature. These are 3-phenyl-1,3-benzoxazine-2,4-dione[2,3] itself, prepared from salicylanilide and ethyl chloroformate, and 3-(4-bromophenyl)-1,3-benzoxazine-2,4-dione,[4] prepared by fusing phenyl salicylate with 3-(*p*-bromophenyl)-2-methyl-1-phenyl-2-thiopseudourea and hydrolyzing the resulting intermediate.[5]

Treatment of a series of halo- and nitrosalicylanilides with ethyl chloroformate in pyridine–acetonitrile[6] yielded the corresponding benzoxazinediones (Table I)



yield, furnishing products easily purified by recrystallization.

The infrared spectra of a number of the benzoxazinediones were examined. As expected, two carbonyl absorptions characteristic of cyclic imides were observed. The bands occurred at 1690 cm.$^{-1}$, assigned to the carbonyl of 6-membered lactams, and at 1760 cm.$^{-1}$, assigned to the carbonyl of 6-membered lactones.[7]

The bacteriostatic activity of a number of these compounds against *Staphylococcus aureus in vitro* was determined[8] (Table II). The presence of at least two halogens is required for optimum activity, provided that both the 2- and 5-positions of the 3-phenyl ring are not substituted. The activity parallels that of the corresponding salicylanilides except for compounds 1 and 3, for which the parent anilides were more active, and compound 8, which is more active than its parent anilide.

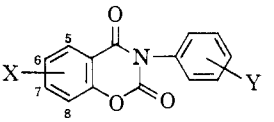
Experimental[9]

Salicylanilides.—The substituted salicylanilides corresponding to compounds 2, 3, 6 to 12, 14, 15, 17 and 18 (Table I) have been described in the literature.[1,10] The anilides required for the preparation of compounds 4 and 16 were purchased from the Aldrich Chemical Co., Inc.

2',3'-Dichlorosalicylanilide.—This anilide was prepared from phenyl salicylate and 2,3-dichloroaniline by a procedure employed for the preparation of similar salicylanilides[10b]; m.p. 222–224° (from chlorobenzene), yield, 76%.

TABLE I

3-PHENYL-1,3-BENZOXAZINE-2,4-DIONES



Compound[c]	X	Y	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Halogen, % Calcd.	Halogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1			47	254–255[a]	$C_{14}H_9NO_3$							5.86	5.76
2		4-Cl	69	245–246	$C_{14}H_8ClNO_3$	61.4	61.1	2.95	2.90	13.0	13.1	5.12	5.10
3		4-Br	69	251–252[b]	$C_{14}H_8BrNO_3$	52.9	52.9	2.54	2.60	25.1	25.4	4.40	4.30
4	6-Cl		61	285–286	$C_{14}H_8ClNO_3$	61.4	61.7	2.95	3.05	13.0	13.1	5.12	5.00
5		2,3-Cl_2	67	195–197	$C_{14}H_7Cl_2NO_3$	54.6	54.8	2.29	2.49	23.0	23.1	4.55	4.53
6		2,4-Cl_2	70	166–167	$C_{14}H_7Cl_2NO_3$	54.6	54.5	2.29	2.44	23.0	23.0	4.55	4.31
7		2,5-Cl_2	37	176–177	$C_{14}H_7Cl_2NO_3$	54.6	54.7	2.29	2.30	23.0	23.1	4.55	4.50
8		3,4-Cl_2	77	193–195	$C_{14}H_7Cl_2NO_3$	54.6	54.5	2.29	2.50	23.0	23.4	4.55	4.71
9		3,5-Cl_2	83	183–184	$C_{14}H_7Cl_2NO_3$	54.6	54.7	2.29	2.57	23.0	23.3	4.55	4.70
10	6,8-Cl_2		73	234–235	$C_{14}H_7Cl_2NO_3$	54.6	54.7	2.29	2.39	23.0	22.8	4.55	4.45
11	6-Cl	4-Cl	30	221–222	$C_{14}H_7Cl_2NO_3$	54.6	54.8	2.29	2.38	23.0	23.2	4.55	4.44
12	6-Br	4-Cl	73	217–218	$C_{14}H_7BrClNO_3$	47.7	47.9	2.00	1.99			3.97	4.01
13		2,4,5-Cl_3	70	185–186	$C_{14}H_6Cl_3NO_3$	49.1	48.9	1.77	2.03	31.1	30.8	4.09	4.04
14	6-Cl	3,4-Cl_2	80	219–220	$C_{14}H_6Cl_3NO_3$	49.1	48.8	1.77	1.93	31.1	31.2	4.09	4.20
15	6,8-Br_2	4-Br	79	300–301	$C_{14}H_6Br_3NO_3$	35.3	35.1	1.27	1.20	50.4	50.3	2.94	3.03
16	6,8-Cl_2	3,4-Cl_2	69	261–262	$C_{14}H_5Cl_4NO_3$	44.6	44.9	1.34	1.52	37.6	37.4	3.72	3.62
17	6-NO_2	3,4-Cl_2	79	234–235	$C_{14}H_6Cl_2N_2O_5$	47.6	47.6	1.71	1.89	20.1	20.1	7.94	7.90
18	8-NO_2	3,4-Cl_2	47	166–168	$C_{14}H_6Cl_2N_2O_5$	47.6	47.5	1.71	2.18	20.1	20.3	7.94	7.66

[a] Lit.,[2] m.p. 246°. [b] Lit.,[4] m.p. 214°; only a nitrogen analysis was reported. [c] Compound 1 was recrystallized from acetone; 2, 3, 5, 7, 8, 9, 10, 12, 15, 16 and 18 from toluene; 4 from dimethylformamide; 6 and 13 from toluene–methylcyclohexane; 11 from ethyl acetate; 14 from chlorobenzene and 17 from dimethylformamide–water.

via the unisolated intermediate carbonic esters. In general, the cyclization occurred smoothly and in good

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(4) J. F. Deck and F. B. Dains, *J. Am. Chem. Soc.*, **55**, 4986 (1933).

(5) Since the melting point of our 3-(4-bromophenyl)-1,3-benzoxazine-2,4-dione (compound 3) differed by about 40° from the reported[4] value, we also employed the fusion method and obtained in low yield a product (m.p. 212–222°) which, according to elemental analysis and the infrared spectrum, was a mixture of 3-phenyl- and 3-(4-bromophenyl)-1,3-benzoxazine-2,4-dione.

TABLE II
BACTERIOSTATIC ACTIVITY OF 1,3-BENZOXAZINE-2,4-DIONES

Number[a]	Substituents	Concentration for inhibition of *S.a.*[b]
1	3-Phenyl	T
3	3-(4-Bromophenyl)	T
6	3-(2,4-Dichlorophenyl)	M
7	3-(2,5-Dichlorophenyl)	+
8	3-(3,4-Dichlorophenyl)	M
9	3-(3,5-Dichlorophenyl)	M
10	6,8-Dichloro-3-phenyl	M
12	6-Bromo-3-(4-chlorophenyl)	M
13	3-(2,4,5-Trichlorophenyl)	+
14	6-Chloro-3-(3,4-dichlorophenyl)	M
16	6,8-Dichloro-3-(3,4-dichlorophenyl)	M
17	3-(3,4-Dichlorophenyl)-6-nitro	M
18	3-(3,4-Dichlorophenyl)-8-nitro	M

[a] These numbers correspond to those in Table I. [b] *S.a.* = *Staphylococcus aureus;* + represents growth at a concentration of 1×10^3. T and M represent no growth at a concentration of 1×10^3 and 1×10^6, respectively.

Anal. Calcd. for $C_{13}H_9Cl_2NO_2$: Cl, 25.1; N, 4.95. Found: Cl, 25.2; N, 4.80.

2',4',5'-Trichlorosalicylanilide.—This anilide was prepared in essentially the same manner as the preceding compound; m.p. 280–281° (from dimethylformamide-ethanol); yield, 63%.

Anal. Calcd. for $C_{13}H_8Cl_3NO_2$: N, 4.43. Found: N, 4.60.

3-Phenyl-1,3-benzoxazine-2,4-diones (Table I).—A solution or a suspension of 0.02–0.1 mole of the salicylanilide in 50 ml. of pyridine and 30 ml. of acetonitrile was stirred at 2–5° during the dropwise addition of 1.1 times the equimolar quantity of ethyl chloroformate. Stirring was continued while the temperature was gradually increased to 120–125° over a period of 1–2 hr. and 60 ml. of distillate was collected in a Barrett trap. The residue was cooled, and before it solidified 150 ml. of water and 5 ml. of concd. hydrochloric acid were added slowly with stirring and further cooling. After thoroughly stirring the mixture, the crude product was collected, washed with water, dried and recrystallized after decolorization with activated carbon, if required.

The infrared spectra (Nujol mull) of compounds 1, 3, 15 and 16 were obtained using a Beckman IR-5 spectrophotometer. Examination of the spectra revealed the presence of two carbonyl absorptions at 1690 and 1760 cm.$^{-1}$ and the absence of the characteristic NH and OH bands of the salicylanilides.

Acknowledgment.—We wish to thank Mr. P. D. McDonald for the microbiological evaluations and Messrs. John L. O'Sullivan and Ottmar Kring for part of the analytical data.

(6) S. L. Shapiro, I. M. Rose, and L. Freedman, *J. Am. Chem. Soc.*, **79**, 2811 (1957).

(7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 176, 205, 221.

(8) For the test procedure, see D. J. Beaver, D. P. Roman, and P. J. Stoffel, *J. Am. Chem. Soc.*, **79**, 1236 (1957).

(9) All melting points, taken on a Fisher–Johns Melting Point Apparatus, are corrected.

(10) (a) R. Anschütz and H. Mehring, *Ann.*, **346**, 300 (1906); (b) C. F. H. Allen and J. Van Allan, *Org. Syntheses*, Coll. Vol. III, 765 (1955); (c) V. E. Schraufstätter, W. Meiser, and R. Gönnert, *Z. Naturforsch.*, **16b** (2). 95 (1961).

4,6-Diamino-1-alkyl-1,2-dihydro-*s*-triazines

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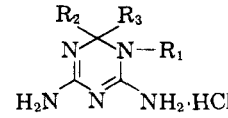
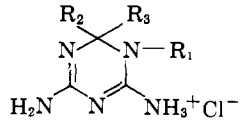
Preparative methods for 4,6-diamino-1-aryl-1,2-dihydro-2,2-disubstituted-*s*-triazines (Ia) are well documented in the literature.

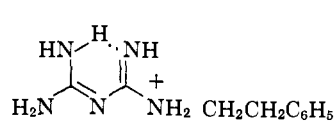


Ia, R_1 = aryl
Ib, R_1 = alkyl

These 1-aryl derivatives of I have been prepared from N^1-aryl-substituted biguanides and aldehydes or ketones under a variety of conditions.[1,2,3] Products from these reactions are reported to have antimalarial,[1,4] antimicrobial,[5] antiparasitic,[6] antitumor[7] activity and to be plant growth inhibitors.[8] This interesting spectrum of activity, together with their possible steric relationship to biguanides with antidiabetic activity (*vide infra*), prompted an investigation of the preparation of the previously unknown[9,10] 4,6-diamino-1-alkyl-1,2-dihydro-2,2-disubstituted-*s*-triazines (Ib). These compounds were then tested for hypoglycemic activity since they were thought to resemble sterically the hydrogen bonded, cyclic structure proposed[11] for a known antidiabetic drug, phenethylbiguanide hydrochloride (II).

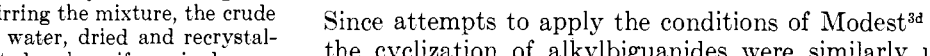


Ib

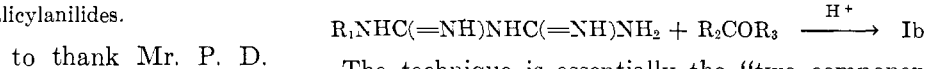


II

Modest[3] has reported a convenient synthetic technique for the 1-aryl-1,2-dihydro-*s*-triazines Ia but was unsuccessful[3a] in an attempt to prepare the 1-alkyl compounds Ib.



Since attempts to apply the conditions of Modest[3d] to the cyclization of alkylbiguanides were similarly unsuccessful, a variety of other conditions were studied. This has resulted in the successful synthesis of Ib from N^1-alkylbiguanides and aldehydes or ketones.



The technique is essentially the "two component" method of Modest[3d]; however, continuous removal of water from the reaction system and careful control of acid concentration (15–20% excess over 1 *M* equivalent was optimal) were found to be critical factors in this reaction. All compounds of type Ib were prepared by a similar technique as illustrated in the experimental

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(2) S. Birtwell, F. H. S.Curd, J. A. Hendry, and F L. Rose, *J. Chem. Soc.*, 1645 (1948).

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(8) L. Rudenberg, G. E. Foley, and W. D. Winter, Jr., *Science*, **121**, 899 (1955).

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(11) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 2220 (1959).