3,4,5,6-Tetrahydro-1-[2-(4-hydroxy-4-phenyl-1-piperidyl)-ethyl]-1-benzazocin-2(1H)-one Hydrochloride (21).—To 10.0 g (0.057 mole) of 3,4,5,6-tetrahydrobenzazocin-2(1H)-one in 100 ml of xylene was carefully added 3.0 g of NaH with stirring. The reaction mixture was then refluxed with stirring for 2 hr. To the mixture was added 3.0 g of NaH and 19.2 g (0.06 mole) of 1-(2-chlorethyl)-4-hydroxy-4-phenylpiperidine hydrobromide. The reaction mixture was stirred under reflux for 8 hr, then treated with H_2O and $CHCl_3$. The organic solvents were concentrated *in vacuo* leaving an oily residue. The starting amide was removed by vacuum distillation; the remaining residue weighed 17.0 g. The hydrochloride was prepared by adding excess HCl in *i*-PrOH to a solution of the base in MeOH. Upon addition of Et_2O, a solid formed which was recrystallized three times from MeOH–Et_2O; yield 3.5 g, mp 237–238°.

1-[3-(4-*p*-Fluorophenyl-1-piperazyl)propyl]-3,4-dihydro-7-hydroxycarbostyril Hemioxalate (15).—To 15.0 g (0.032 mole) of 7-benzyloxy-1-[3-(4-*p*-fluorophenyl-1-piperazyl)propyl]-3,4-dihydrocarbostyril in 200 ml of absolute EtOH was added 2.5 g of 10% Pd–C and the mixture was hydrogenated at 3.5 kg/cm² for 2 hr. The solution was filtered to remove the catalyst and the filtrate was concentrated *in vacuo* leaving an oil. The oxalate was prepared by adding 3.0 g (0.034 mole) of oxalic acid in Et_2O to 13.0 g (0.034 mole) of the free base. A solid material was obtained which was recrystallized from MeOH–Et_2O; yield 5.0 g, mp 209–210°.

Acknowledgment.—The authors wish to thank Dr. Dale Stauffer and associates for the analytical services. We are indebted to Messrs. Ted Leipzig, Richard Kulp, and Fred Ward for the preparation of intermediates.

Synthesis and Analgetic Activity of Some 1-Substituted 3-Pyrrolidinylanilides and Dihydrobenzoxazinones

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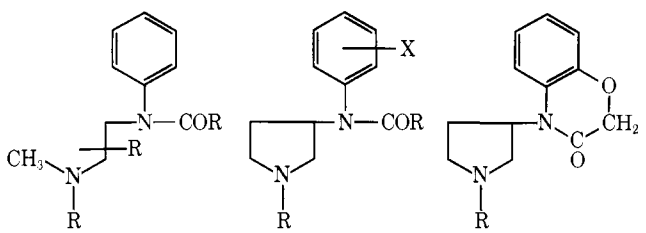
Received December 9, 1968

Some 1-substituted 3-pyrrolidinylanilides and 1-substituted 3-pyrrolidinyl-2H-1,4-benzoxazin-3(4H)-ones have been prepared and tested for analgetic activity. Several of the compounds show moderate to potent activity.

Anilides of the structural type I have been shown to be strong analgetics.[1] In this paper the preparation and analgetic properties of a series of 1-substituted 3-pyrrolidinylanilides (II) and dihydrobenzoxazinones (III) are described. These structures can be viewed as cyclized versions of I.



I II III

Chemistry.—The synthetic routes used to obtain these compounds are shown in Chart I. The anilinopyrrolidines (V) were prepared by the nucleophilic displacement of the toluenesulfonate ester of a 3-pyrrolidinol or a 3-bromopyrrolidine (IV) by an aniline derivative. This tosylate displacement reaction has been previously reported.[2] The properties of new compounds are given in Table I. The N-substituent was varied by starting with the appropriate 1-substituted pyrrolidine (IV) or by catalytically hydrogenating the 1-benzylpyrrolidine (V, R = benzyl) to the corresponding secondary amine and alkylating with the appropriate alkyl halide. Treatment of the anilinopyrrolidines with an acid chloride or anhydride gave the anilides (VI) in good yield. The hydroxyanilides (VI, X = OH) were prepared by the reaction of the hydroxyanilinopyrrolidines and 2 equiv of propionic anhydride or propionyl chloride and subsequent hydrolysis of the ester with dilute NaOH. The first equivalent of anhydride or acid chloride gave a mixture of ester and amide as shown by ir and nmr spectra.

The dihydrobenzoxazinones (IX) were prepared by the reaction of the 2-hydroxyanilinopyrrolidines (VII) with chloroacetyl chloride and treatment of the resulting amide (VIII) with base.

The experimental details are given in Tables I–III and in the Experimental Section.

The ir and nmr spectra of the compounds described are consistent with the proposed structures. It is interesting to note, however, that the aromatic hydrogen at position 8 (*ortho* to N) in **21**, **22**, **24**, and **25** are at unusually low-field positions (τ 2.3–1.9) for compounds of this type. Molecular models suggest that the *o*-hydrogen of these compounds is crowded into close proximity with the nitrogen of the pyrrolidine ring, thereby experiencing a deshielding influence from the unshared electrons on the N. Related proximity effects have been described.[3]

Pharmacology.—Compounds were tested for analgetic activity in female mice (ICR strain) using a modification of the method of Nilsen[4] as previously described.[5]

Toxicity was estimated in female mice of the same strain, using two animals per dose level. The results of these tests are summarized in Table IV. Some of the compounds were also investigated for analgetic activity using the method of Randall and Selitto.[6] In

(1) R. A. Hardy, Jr., and M. G. Howell in "Analgetics," G. deStevens, Ed., Academic Press Inc., New York, N. Y., 1965, Chapter V.

(2) W. J. Welstead, Jr., J. P. DaVanzo, G. C. Helsley, C. D. Lunsford, and C. R. Taylor, Jr., *J. Med. Chem.*, **10**, 1015 (1967).

(3) M. J. T. Robinson, *Tetrahedron Letters*, 1153 (1968).

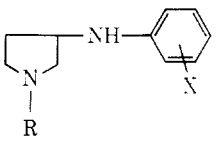
(4) P. Nilsen, *Acta Pharmacol. Toxicol.*, **18**, 10 (1961).

(5) G. C. Helsley, J. A. Richman, C. D. Lunsford, H. Jenkins, R. P. Mays, W. H. Funderburk, and D. N. Johnson, *J. Med. Chem.*, **11**, 472 (1968).

(6) L. O. Randall and J. J. Selitto, *Arch. Intern. Pharmacodyn.*, **111**, 409 (1957).

TABLE I

ANILINOPYRROLIDINES

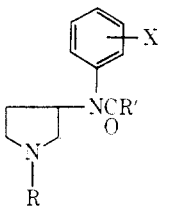


R	X	Prepn[a] method	% yield	Mp, °C	Recrystn solvent[b]	Formula[c]
C_2H_5	3-OH	A	50	168–169	Mi	$C_{12}H_{18}N_2O$
C_2H_5	3-CF_3	A	23	115–116	I	$C_{19}H_{20}F_3N_3O_3S$[d]
$CH_2C_6H_5$	3-OH	B	13	127–128	B	$C_{17}H_{20}N_2O$
$CH_2C_6H_5$	2-OH	B	22	115–116	B	$C_{17}H_{20}N_2O$
$CH_2CH_2OC_6H_5$	H	C	58	150–151	I	$C_{22}H_{26}N_2O_5$[e]
$CH_2CH_2OC_6H_4$-2-OCH_3	H	C	66	114–116	I–Ip	$C_{23}H_{28}N_2O_5$[e]
$CH_2CH_2COC_6H_5$	H	D	68	175–178	I	$C_{19}H_{24}Cl_2N_2O$[f]
$CH_2CH_2COC_6H_5$	2-OCH_3	D	87	192–194	E	$C_{20}H_{26}Cl_2N_2O_2$[f]

[a] See Experimental Section. [b] Mi = methyl isobutyl ketone, I = *i*-PrOH, B = C_6H_6, Ip = *i*-Pr_2O, E = EtOH. [c] All compounds analyzed for C, H, N. [d] N-Cyclohexylsulfamate. [e] Fumarate. [f] Dihydrochloride.

TABLE II

3-PYRROLIDINYLANILIDES



No.	R	R′	X	Prepn[a] method	Yield, %	Mp or bp (mm), °C	Recrystn solvent[b]	Formula[c]
1	CH_3	CH_3	H	F	72	110–113	I	$C_{17}H_{22}N_2O_5$[d]
2	CH_3	C_2H_5	H	F	71	133–135	I	$C_{18}H_{24}N_2O_5$[d]
3	CH_3	$CH_2C_6H_5$	H	F	59	135–140 (0.04)		$C_{19}H_{22}N_2O$[e]
4	CH_3	$CH_2OC_6H_5$	H	F	63	138–139	I–Ip	$C_{21}H_{24}N_2O_6$[f]
5	CH_3	C_6H_5	H	F	58	98–99	Ip	$C_{18}H_{20}N_2O$
6	CH_3	$CH_2OC_6H_4$-4-Cl	H	F	78	105–108	I–Ip	$C_{23}H_{25}ClN_2O_6$[g]
7	C_2H_5	C_2H_5	3-CF_3	E	85	155–156	I–Ip	$C_{20}H_{25}F_3N_2O_5$[d]
8	CH_3	C_6H_4-4-Cl	H	F	73	124–126	I–Ip	$C_{22}H_{23}ClN_2O_5$[d]
9	$CH_2CH{=}CH_2$	C_2H_5	H	F	66	139–141	I–Ip	$C_{18}H_{24}N_2O_5$[f]
10	$CH_2C_6H_5$	C_2H_5	H	F	78	180 (0.02)		$C_{20}H_{24}N_2O$
11	$CH_2C_6H_5$	C_2H_5	3-OH	G	29	123–125	Ip–B	$C_{20}H_{24}N_2O_2$
12	$CH_2C_6H_5$	C_2H_5	2-OH	G	60	92–94	I–Ip	$C_{21}H_{26}N_2O_6$[f]
13	$CH_2C_6H_5$	C_2H_5	2-OCH_3	F	90	190 (0.03)		$C_{21}H_{26}N_2O_2$
14	$CH_2CH_2C_6H_5$	C_2H_5	H	E	59	105–108	I–Ip	$C_{25}H_{30}N_2O_5$[d]
15	$CH_2CH_2OC_6H_5$	C_2H_5	H	E	52	115–118	I–Ip	$C_{21}H_{27}ClN_2O_2$[h]
16	$CH_2CH_2OC_6H_5$	C_2H_5	2-OCH_3	F	52	*i*		$C_{22}H_{28}N_2O_3$
17	$CH_2CH_2OC_6H_4$-2-OCH_3	C_2H_5	H	E	49	192–194 (0.02)		$C_{22}H_{28}N_2O_3$
18	$CH_2CH_2COC_6H_5$	C_2H_5	H	F	65	72–74	O	$C_{22}H_{26}N_2O_2$
19	$CH_2CH_2COC_6H_5$	C_2H_5	2-OCH_3	F	90	*i*		$C_{23}H_{28}N_2O_3$[k]
20	H	C_2H_5	2-OCH_3	*j*	41	130–133	EA–M	$C_{18}H_{24}N_2O_6$[d]

[a] See Experimental section. [b] I = *i*-PrOH, Ip = *i*-Pr_2O, B = C_6H_6, O = isooctane, EA = EtOAc, M = MeOH. [c] All compounds analyzed for C, H, N. [d] Fumarate. [e] C: calcd, 77.52; found, 76.88. [f] Oxalate. [g] Maleate. [h] Hydrochloride. [i] Oil purified by column chromatography on Florisil, eluted with C_6H_6–Me_2CO. [j] Catalytic reduction (Pd–C) of corresponding N-benzyl compound (**21**). [k] C: calcd, 72.60; found, 72.07.

most instances the results were comparable to those obtained using the Nilsen method.

The most active compounds were those in which the pyrrolidine N substituent (R) was phenethyl, *o*-methoxyphenoxyethyl, or benzoylethyl (**14**, **17**, **18**).

The anilides containing a hydroxy or methoxy substituent (**11**–**13**, **16**, **19**) were either equivalent to or less potent than the corresponding unsubstituted compounds (**10**, **15**, 18).

The *p*-chlorophenyl compounds (**6**, **8**) showed moderte activity and the corresponding unsubstituted compounds (**4**, **5**) showed very little activity. Additional synthetic work aimed at developing structure–activity relationships concerning the acyl group (R′) is in progress.

The benzoxazinones (**21**–**25**) showed weak or no analgetic activity at the doses tested.

At effective doses these compounds produced neither sedation nor depression. Certain compounds, however, at higher doses produced excitement, piloerection, and Straub tail.

Experimental Section

General procedures, in most cases, are given below for the preparation of compounds described in this paper. Analyses, yields, and physical properties are recorded in the tables and

CHART I

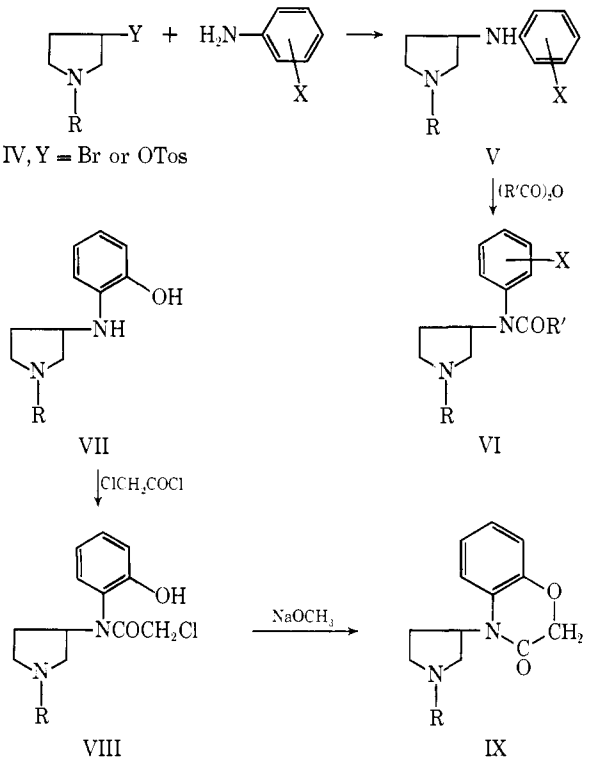
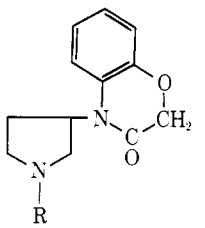


TABLE III

3-PYRROLIDINYLDIHYDROBENZOXAZINONES



No.	R	% yield	Mp or bp (mm), C	Formula[c]
21	C_2H_5	31	155–156[a]	$C_{18}H_{22}N_2O_6$[d]
22	$CH_2C_6H_5$	50	188–191 (0.01)	$C_{19}H_{20}N_2O_2$
23	H	94	216–217[a]	$C_{12}H_{15}ClN_2O_2$[e]
24	$CH_2CH_2C_6H_5$	65	92–94[b]	$C_{22}H_{24}N_2O_6$[f]
25	$CH_2CH_2COC_6H_5$	65	107–111[b]	$C_{23}H_{24}N_2O_7$[f]

[a] Recrystallized from *i*-PrOH–*i*-Pr_2O. [b] Recrystallized from *i*-PrOH. [c] All compounds analyzed for C, H, N. [d] Fumarate. [e] Hydrochloride. [f] Oxalate.

significant variations in the procedures are noted in the table footnotes. Temperatures are uncorrected.

3-Anilinopyrrolidines (Table I). Method A. Tosylate Displacement.—The procedure was essentially the same as that previously reported.[2]

Method B. Bromide Displacement.—A stirred mixture of 1.0 mole of the 3-bromopyrrolidine,[7] 1.0 mole of the hydroxyaniline and 1.0 mole of K_2CO_3 in 1 l. of PhMe was heated at reflux for 16 hr. The reaction mixture was filtered hot and the filtrate was extracted with 500 ml of 3 *N* NaOH. The basic layer was separated, acidified with 6 *N* HCl, and extracted (Et_2O). After the acidic layer was neutralized with 10% $NaHCO_3$, it was extracted with $CHCl_3$. The combined extracts were washed (H_2O) and dried ($MgSO_4$), and the solvent was evaporated. The crude products were purified by recrystallization.

Method C. Alkylation of 3-Anilinopyrrolidine.—A mixture of 0.1 mole of a 3-anilinopyrrolidine,[2] 0.1 mole of the alkyl bromide, 20 g of K_2CO_3, and 100 ml of EtOH was stirred and heated at reflux for 16 hr. After the solvent was evaporated at reduced pressure, the residue was treated with dilute NaOH and extracted (Et_2O). The combined extracts were washed (H_2O) and dried ($MgSO_4$), and the solvent was evaporated. The crude products were purified by conversion to a solid addition salt followed by recrystallization.

(7) D. C. Ruopp, F. A. E. Schilling, and B. B. Brown, *J. Pharm. Sci.*, **56**, 1038 (1967).

TABLE IV

ANALGETIC ACTIVITY AND APPROXIMATE TOXICITY OF TEST COMPOUNDS IN FEMALE MICE

No.	No. analgetic/ no. tested[a]	ED_{50} (95% confid limits), mg/kg ip	Toxic range,[b] mg/kg ip
1	1/5		160–320
2	3/5		160–320
3	0/5		80–160
4	2/10		80–160
5	1/5		80–160
6	7/10	16.5 (9.2–29.6)	80–160
7	2/10		80–160
8	10/10	5.2 (3.0–9.9)	80–160
9	4/5	8.0 (3.8–16.8)	160–320
10	4/5	5.7 (4.0–8.2)	80–160
11	4/5	10.1 (6.3–16.2)	80–160
12	2/5		40–160
13	3/5		80–160
14	5/5	2.0 (1.0–4.0)	40–80
15	6/9	14.2 (9.6–20.9)	40–160
16	9/10		80–160
17	5/5	3.4 (1.7–6.7)	80–160
18	5/5	0.5 (0.2–1.1)	80–160
19	4/5		80–160
20	0/5		80–160
21	2/5, 4/5[c]		80–160
22	0/5		160–320
23	0/5		160–320
24	0/5, 2/5[c]		80–320
25	0/5		40–80
Meperidine	5/5	6.4 (4.3–9.6)	
Morphine	5/5	1.7 (1.0–2.9)	

[a] 15 min after injection of 20 mg/kg ip. [b] Two doses which were toxic in 0 and 100% of the animals. [c] 15 min after injection of 40 mg/kg ip.

Method D. Amine Exchange.—A mixture of 0.06 mole of 2-benzoylethyldimethylamine hydrochloride, 0.06 mole of the anilinopyrrolidine, and 10 g of K_2CO_3 was stirred together in DMF while N_2 was bubbled through the mixture to remove the dimethylamine as it was formed. After 24 hr 250 ml of H_2O was added to the mixture and the oily product was extracted into C_6H_6. The combined extracts were washed (H_2O) and dried ($MgSO_4$), and the solvent was evaporated. The products were purified by conversion to a solid addition salt followed by recrystallization.

3-Pyrrolidinylanilides (Table II). Method E. Acid Anhydride Reaction.—A mixture of 0.04 mole of the 3-anilinopyrrolidine, 0.05 mole of the acid anhydride, and 50 ml of C_6H_6 was refluxed for 4 hr, cooled, and washed (10% $NaHCO_3$, H_2O). The solution was dried (Na_2SO_4) and the solvent was evaporated. The amides were purified by distillation and/or conversion to a solid addition salt.

Method F. Acid Chloride Reaction.—A stirred mixture of 0.06 mole of the 3-anilinopyrrolidine, and 18 g of K_2CO_3 in 100 ml of $CHCl_3$ was treated with 0.07 mole of the acid chloride in 50 ml of $CHCl_3$. After addition the mixture was stirred 2 hr then treated with 200 ml of H_2O and stirred another 1 hr. The $CHCl_3$ layer was separated and dried ($MgSO_4$) and the solvent was evaporated. The crude products were purified as indicated in Table II.

Method G. Diacylation Reaction.—To a stirred solution of 0.06 mole of the 3-hydroxyanilinopyrrolidine in 100 ml of $CHCl_3$ (below 0°) was added slowly 0.12 mole of EtCOCl (after the first equivalent of acid chloride was added an aliquot of the mixture was withdrawn, and shown to be a mixture of ester and amide by nmr and ir studies). After the addition was complete, the reaction mixture was allowed to come to room temperature and was heated at reflux for several hours. The solution was then cooled, filtered, extracted with 10% $NaHCO_3$, washed (H_2O), and dried ($MgSO_4$) and the solvent was evaporated. The residual oil was treated with 250 ml of 1 *N* NaOH containing about 20% EtOH. The mixture was stirred for 1 hr at ambient temperature, made

acidic with 6 *N* HCl, treated with 10% $NaHCO_3$, and finally extracted with C_6H_6. The combined extracts were washed with H_2O and dried ($MgSO_4$) and the solvent was evaporated. The crude products were purified by recrystallization as the free base or acid addition salt.

4-(1-Substituted 3-Pyrrolidinyl)-2H-1,4-benzoxazin-3(4H)-ones (Table III).—To a stirred solution of 0.10 mole of the 1-substituted 3-(*o*-hydroxyanilino)pyrrolidine in 250 ml of $CHCl_3$ maintained at 0–5° was added slowly a solution of 0.10 mole of chloroacetyl chloride in 50 ml of $CHCl_3$. After the addition was complete the mixture was allowed to warm to room temperature. The solvent was then evaporated at reduced pressure; the residual oil was dissolved in 500 ml of *i*-PrOH and treated with 0.20 mole of NaOMe. The mixture was stirred and heated at reflux for 16 hr, cooled, and filtered. After the solvent was evaporated, the residual oil was taken up in *i*-Pr_2O, washed with 1 *N* NaOH and H_2O, and dried ($MgSO_4$) and the solvent was evaporated. The products were purified by distillation or conversion to a salt.

3-Pyrrolidinyl-2H-1,4-benzoxazin-3(4H)-one (23).—A solution of 15 g of 4-(1-benzyl-3-pyrrolidinyl)-2H-1,4-benzoxazin-3(4H)-one in 200 ml of 95% EtOH was reduced catalytically with 5 g of 10% Pd–C. The mixture was heated at 70° and shaken with H_2 until 1 equiv of H_2 was absorbed (*ca.* 2 hr). After cooling, the suspension was filtered and the solvent was evaporated. The product was purified by conversion to a salt followed by recrystallization.

4-[1-(2-Phenylethyl)-3-pyrrolidinyl]-2H-1,4-benzoxazin-3(4H)-one (24).—A mixture of 0.04 mole of **31** (Table III), 0.04 mole of phenethyl bromide, 15 g of K_2CO_3, and 100 ml of dry PhMe was stirred and heated at reflux for 16 hr, cooled, and treated with 100 ml of H_2O. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), and filtered and the solvent was evaporated. The residual oil was purified by conversion to a solid salt followed by recrystallization.

4-[1-(2-Benzoylethyl)-3-pyrrolidinyl]-2H-1,4-benzoxazin-3(4H)-one (25).—Compound **23** was treated with 2-benzoylethyldimethylamine hydrochloride as previously described (Method D, Amine Exchange).

Acknowledgment.—The authors thank Mr. Ying-Ho Chen for preparation of two of the compounds, Mr. Ashby Johnson for nmr spectra, and Mrs. Marianne H. Foxwell for technical assistance in pharmacological testing.

Heterocyclic Mesoionic Structures, a Novel Class of Monoamine Oxidase Inhibitors. II. Arylanhydro-1,2,3-thiadiazolium Hydroxides

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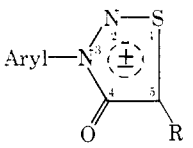
Received February 20, 1969

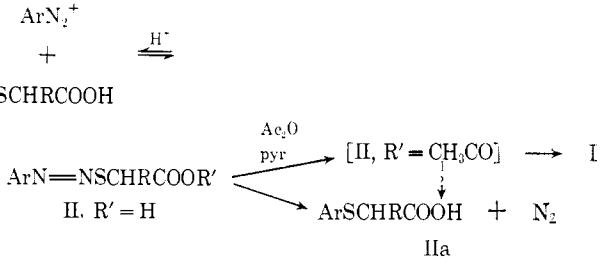
The preparation and monoamine oxidase inhibitory activity of a series of arylanhydro-1,2,3-thiadiazolium hydroxides (I) is described. A visualization of enzyme–inhibitor interaction is presented, as well as an analysis of the structural features controlling the mode of enzyme inhibition. Those inhibitors showing noncompetitive inhibitory activity *in vitro* were shown also to be active inhibitors of the enzyme *in vivo*, while competitive inhibitors were inactive *in vivo*. These observations support and extend those made in a previous study of mesoionic compounds, the N-arylsydnones.

The inhibition of the enzyme, monoamine oxidase (MAO), has previously been reported[1] for the heterocyclic mesoionic N-arylsydnones. This report is an account of the preparation of anhydro-3-aryl-4-hydroxy-1,2,3-thiadiazolium hydroxides (I),[2] and a discussion of the structure–activity requirements for the inhibition of MAO.



I

Anhydro-1,2,3-thiadiazolium hydroxides were prepared *via* the reported sequence.[3,4] With the exception of 5-methyl homologs, 5-substituted derivatives of I were obtained by the appropriate substitution reaction on the parent anhydro-1,2,3-thiadiazolium hydroxide.[3] The limiting factor in the preparation of I was the stability of the intermediate arylazothioacetic acid II. It was previously reported that polysubstituted and especially *ortho*-substituted phenyl derivatives of either I or II could not be prepared; these restrictions did not apply if conditions were chosen which minimized two side reactions of II: (1) acid-catalyzed cleavage to diazonium salt,[5] and (2) thermal elimination of N_2 to yield carboxymethyl aryl sulfides IIa.[6] The stability of II increased with increasing electron-releasing potential in the phenyl ring, although this favorable trend was compromised by retardation of the rate of cyclization of *ortho*-substituted analogs. Electronegative substituents (halogen, NO_2, CF_3) conjugated (*para, ortho*) with the diazo sulfide moiety depressed cyclization to I and enhanced (to the point of explosiveness) formation of IIa; consequently, the corresponding cyclic derivatives were difficult to prepare unless the phenyl ring contained additional con-



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(2) The analysis of infrared, ultraviolet, and nuclear magnetic resonance spectra supporting the assignment of a mesoionic structure to I will be discussed in a subsequent publication (D. P. Cameron, in preparation).

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