2-amino-5-Aryl-2-oxazolines. Potent New Anorectic Agents

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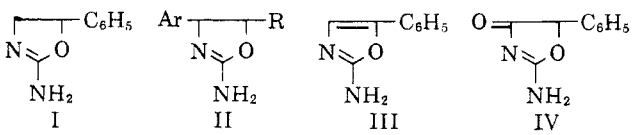
A series of 2-amino-5-aryl-2-oxazolines was found to have potent appetite suppressant activity. Methods of synthesis, chemical behavior, and structure–activity relationships for these compounds are described.

In pursuit of our interests in cyclic pseudoureas as potential pharmacological agents,[1] we prepared several representative substituted 2-amino-2-oxazolines. One of these compounds, 2-amino-5-phenyl-2-oxazoline (I), was shown in preliminary pharmacological testing to have potent anorectic and interesting CNS stimulant activity. These results encouraged us to expand the investigation which forms the subject of this report.

Chemistry.—Very few 2-amino-2-oxazolines are reported in the literature. Although the parent structure has been known since 1889,[2] there has been relatively little work done with this class of compounds.[3] There are several reports in the literature describing 2-amino-4-aryl-2-oxazolines[3,4] such as II (R = H, CH_3; Ar = C_6H_5, 4-$CH_3OC_6H_4$, 3,4-$(CH_2)_2OC_6H_3$, etc.), but



no 2-amino-5-aryl-2-oxazolines have been described. Known related compounds such as 2-amino-5-phenyloxazole (III)[5] and 2-amino-5-phenyl-2-oxazolin-4-one (IV)[6] were prepared in the course of this investigation and are included in the structure-activity study.

The preparation of 2-amino-2-oxazolines was conveniently carried out by reaction of the appropriate 1,2-amino alcohol with cyanogen bromide. As has been observed previously,[1,4c,5] the intermediate hydroxycyanamides cyclized spontaneously and were not isolable. A brief study of the reaction was made using the readily available phenylpropanolamine (*dl*-norephedrine) to give *dl-cis*-2-amino-4-methyl-5-phenyl-2-oxazoline (V). The best yields of V were obtained when 1 mole of the amino alcohol was combined in methanol solution at 0–25° with 3 moles of sodium acetate and 1.1 moles of cyanogen bromide. The yields of analytically pure V were in the range of 55–60% although the crude product was obtained in considerably higher (70–80%) yield. Application of this procedure (method A) to other 1-aryl-2-aminoethanols and propanols gave analogous 2-amino-2-oxazolines in comparable yields (see Table I).

For the synthesis of 2-amino-2-oxazolines containing substituents on the 2-amino group, an alternate method was required. Following the classical scheme,[3] the 1,2-amino alcohol was caused to react with the appropriate isocyanate and the resulting hydroxyurea was converted to the chlorourea with thionyl chloride. The chlorourea, without isolation, was then cyclized to the 2-substituted amino-2-oxazoline by boiling in water (method B). The yields and products obtained by this method are also given in Table I.

Many of the amino alcohols used in this work are known compounds. Although a variety of methods for synthesizing 1-aryl-2-aminoethanols are known, we found that lithium aluminum hydride reduction of the aromatic aldehyde cyanohydrin was the most satisfactory laboratory method of preparation for these intermediates. Several 1-aryl-2-aminoethanols were prepared alternatively by catalytic hydrogenation of the nitro alcohol obtained from the aromatic aldehyde and nitromethane. The free amino alcohols tended to carbonate in the air in most cases and as a result were somewhat difficult to characterize. The data are summarized in Table II.

In analogy to the work of Fromm,[5] an attempt to react styrene oxide and sodium cyanamide led to a mixture of products from which a low yield of 2-amino-4-phenyl-2-oxazoline (VI)[4a] was isolated. These results are similar to those of Takeda and Kuroda,[4a] who obtained VI from styrene dibromide and urea. Attempted reaction of styrene oxide with stabilized cyanamide solution[7] and with cyanamide under several conditions failed.

Due to the paucity of information on the chemical behavior of the 2-amino-2-oxazolines, several reactions of the readily available 4-methyl-5-phenyl compound V were briefly investigated. From both boiling *N* hydrochloric acid and *N* sodium hydroxide, V was recovered largely unchanged. Surprisingly, however, the 5-phenyl derivative (I) was hydrolyzed in boiling 0.1 *N* hydrochloric acid and boiling water to (β-hydroxyphenethyl)urea[8] (VII). A small amount of 5-phenyl-2-oxazolidinone (VIII)[9] was also isolated from these hydrolyses.

When a dilute sulfuric acid solution of V was treated with sodium nitrite, the nitrate salt of V precipitated in 35% yield and 50% of V was recovered unchanged from the solution. This resistance to nitrous acid is surpris-

(1) R. R. Wittekind, J. D. Rosenau, and G. I. Poos, *J. Org. Chem.*, **26**, 444 (1961).

(2) S. Gabriel, *Ber.*, **22**, 1137 (1889).

(3) J. W. Cornforth, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p. 384.

(4) (a) J. Takeda and S. Kuroda, *J. Pharm. Japan*, **449**, 561 (1919); (b) L. Birckenbach and M. Linhard, *Ber.*, **64B**, 1076 (1931); (c) G. Fodor and K. Koczka, *J. Chem. Soc.*, 850 (1952).

(5) E. Fromm and R. Kapeller-Adler, *Ann.*, **467**, 240 (1928).

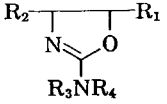
(6) (a) W. Traube and R. Ascher, *Ber.*, **46**, 2077 (1913); (b) see C. F. Howell, N. Q. Quinones, and R. A. Hardy, Jr., *J. Org. Chem.*, **27**, 1679, 1686 (1962), for a recent description of the chemistry and biology of this compound and derivatives.

(7) Aqueous solution obtained from American Cyanamid Co.

(8) C. Mannich and E. Thiele, *Arch. Pharm.*, **253**, 181 (1915).

(9) C. L. Arcus and D. B. Greenwood, *J. Chem. Soc.*, 1937 (1953).

TABLE I: 2-AMINO-2-OXAZOLINES

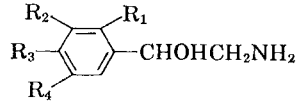


No.	R_1	R_2	R_3	R_4	M.p., °C.	Recryst. from	% Yield	Method	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	ED_{50}, mg./kg.[a]
I	C_6H_5	H	H	H	135–136	C_6H_6	63	A	$C_9H_{10}N_2O$	66.65	6.22	17.27	66.90	6.32	17.45	5.8 (4.1–8.3)
V	C_6H_5	CH_3	H	H	154.5–156	C_6H_6–Petroleum ether	56.5	A	$C_{10}H_{12}N_2O$	68.16	6.86	15.90	68.26	7.13	15.67	8.8 (5.5–14.1)
Va	C_6H_5	CH_3	H	H	148.5–150	C_6H_6	54	A	$C_{10}H_{12}N_2O$	...	...	15.90	...	...	15.85 15.98	7.0 (4.7–10.5)
(+)Va	C_6H_5	CH_3	H	H	177.5–179.5	C_6H_6	59.5	A	$C_{10}H_{12}N_2O$	...	...	15.90	...	...	15.93 16.04	6.9 (2.1–10.3)
XIII	C_6H_5	CH_3	H	CH_3	129–131	C_6H_6–Hexane	83	B	$C_{11}H_{14}N_2O$	...	...	14.73	...	...	14.58	>8
XIV	C_6H_5	CH_3	CH_3	CH_3	B.p. 108° (0.75 mm.)	...	95	B	$C_{12}H_{16}N_2O$	...	...	13.72	...	...	13.42	7
XV[b]	C_6H_5	CH_3	H	C_2H_5	146–147	2-Propanol	60	B	$C_{12}H_{16}N_2O \cdot C_4H_4O_4$	...	...	8.75	...	...	8.77	>10
XVI	C_6H_5	CH_3	H	C_6H_5	130–131	2-Propanol	59	B	$C_{16}H_{16}N_2O$	76.16	6.39	11.10	75.66	6.40	11.15	>30
XVII	C_6H_5	CH_3	H	2-$C_{10}H_7$	181–182	2-Propanol	48	B	$C_{20}H_{18}N_2O$	...	...	9.27	...	...	9.00	>10
XVIII	2-ClC_6H_4	H	H	H	128–130	C_6H_6–Hexane	77	A	$C_9H_9ClN_2O$	...	...	14.25	...	...	14.03	>20
XIX[c]	3-ClC_6H_4	H	H	H	158–160	2-Propanol	52	A	$(C_9H_9ClN_2O)_2 \cdot C_4H_4O_4$	...	...	11.00	...	...	10.61	>5
XX	4-ClC_6H_4	H	H	H	118–119	C_6H_6	54	A	$C_9H_9ClN_2O$	54.97	4.61	14.25	55.24	4.86	14.11	2.5 (1.6–3.9)
XXI	4-ClC_6H_4	H	H	C_6H_5	148–150	2-Propanol	28	B	$C_{15}H_{13}ClN_2O$	66.07	4.82	10.22	65.92	4.88	9.98	>10
XXII	4-ClC_6H_4	H	CH_3	CH_3	B.p. 145° (0.5 mm.)	...	95	B	$C_{11}H_{13}ClN_2O$	58.80	5.83	12.47	58.76	5.96	12.18	>5
XXIII	2,4-$Cl_2C_6H_3$	H	H	H	132–134	C_6H_6	56.5	A	$C_9H_8Cl_2N_2O$	46.78	3.49	12.12	46.90	3.53	12.42	20
XXIV[d]	4-BrC_6H_4	H	H	H	144–145	2-Propanol	63	A	$C_9H_9BrN_2O \cdot C_4H_4O_4$	...	...	7.85	...	...	7.76	4.6 (2.9–7.4)
XXV	4-FC_6H_4	H	H	H	138–139	C_6H_6	42	A	$C_9H_9FN_2O$	59.99	5.04	15.55	59.78	5.18	15.62	1.2 (0.62–2.1)
XXVI	3-$CF_3C_6H_4$	H	H	H	93–94	Et_2O–Hexane	62	A	$C_{10}H_9F_3N_2O$	...	...	12.17	...	...	12.12	4.0 (2.6–6.1)
XXVII	4-$CF_3C_6H_4$	H	H	H	94–96	C_6H_6–Petroleum ether	50	A	$C_{10}H_9F_3N_2O$	...	...	12.17	...	...	12.03	7.0 (5.4–9.1)
XXVIII	4-$CH(CH_3)_2C_6H_4$	H	H	H	158–160	C_6H_6–Et_2O	85	A	$C_{12}H_{16}N_2O$	...	...	13.72	...	...	13.61	>10
XXIX	2-$CH_3OC_6H_4$	H	H	H	102–103	Methylene chloride–Methylcyclohexane	64	A	$C_{10}H_{12}N_2O_2$	...	...	14.58	...	...	14.29	>10
XXX	4-$CH_3OC_6H_4$	H	H	H	135–142	EtOH–Et_2O	50	A	$C_{10}H_{12}N_2O_2$	62.48	6.29	14.58	62.43	6.38	14.40	>30
XXI	3-$C_6H_5CH_2OC_6H_4$	H	H	H	133–135	C_6H_6	91	A	$C_{16}H_{16}N_2O_2$	...	...	10.44	...	...	10.23	>10
XXXII	3,4-$(CH_3O)_2C_6H_3$	H	H	H	119–121	Ethyl acetate	57.5	A	$C_{11}H_{14}N_2O_3$	59.45	6.35	12.60	59.27	6.36	12.59	100
XXXIII	3,4-$CH_2O_2C_6H_3$	H	H	H	178.5–180.5	2-Propanol	61.5	A	$C_{10}H_{10}N_2O_3$	...	...	13.58	...	...	13.46	150
XXXIV	3,4,5-$(CH_3O)_3C_6H_2$	H	H	H	181–183.5	Acetone	44.5	A	$C_{12}H_{16}N_2O_4$	...	...	11.11	...	...	11.05	>100
XXXV	4-$CH_3O_2CC_6H_5$	H	H	H	158–159	Methylene chloride–Et_2O	89	A	$C_{11}H_{12}N_2O_3$	...	...	12.72	...	...	12.55	>10
XXXVI[c]	$C_6H_5OCH_2$	H	H	H	171–173	MeOH	33	A	$(C_{10}H_{12}N_2O_2)_2 \cdot C_4H_4O_4$	52.46	4.95	7.65	52.86	5.25	7.81	30

[a] Oral dose in rats that produces a 50% inhibition of beef broth consumption (ref. 12). Figures in parentheses are 95% confidence limits. The notation >X means there was no inhibition of broth consumption at dose X, the highest level tested. [b] As hydrogen fumarate salt. [c] As fumarate salt. [d] As maleate salt.

TABLE II

2-AMINO-1-ARYLETHANOLS



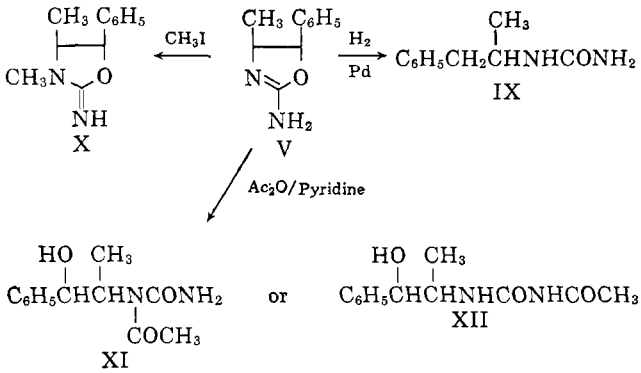
R_1	R_2	R_3	R_4	Characterized as	M.p., °C.	Recryst. from	% Yield	Method	Formula	Analysis Calcd. N	Found N
H	H	H	H	Base	40–41[a]	Et_2O	58, 65	A, B	$C_8H_{11}NO$	...	...
Cl	H	H	H	*p*-Nitrobenzoyl deriv.	196–198[b]	EtOH	57	A	$C_{15}H_{13}ClNO_4$	...	...
H	Cl	H	H	Fumarate	178–179	2-Propanol	35	A	$(C_8H_{10}ClNO)_2 \cdot C_4H_4O_4$	6.32	6.11
H	H	Cl	H	Base	90–92[c]	C_6H_6	70	A	$C_8H_{10}ClNO$	8.16	7.86
Cl	H	Cl	H	Fumarate	183–187 dec.	MeOH	65	A	$(C_8H_9Cl_2NO)_2 \cdot C_4H_4O_4$	5.34	5.28
H	H	Br	H	Base	112–113.5[d]	C_6H_6–Et_2O	48	A	$C_8H_{10}BrNO$	...	...
H	H	F	H	Hydrochloride	210–230[e]	MeOH–Et_2O	57, 50	A, B	$C_8H_{10}FNO \cdot HCl$	...	...
H	CF_3	H	H	Fumarate	175–177	2-Propanol	57	A	$(C_9H_{10}F_3NO_2) \cdot C_4H_4O_4$	5.32	5.09
H	H	CF_3	H	Base	81–82.5	Et_2O–Petroleum ether	59	A	$C_9H_{10}F_3NO$	6.83	6.76
H	H	$(CH_3)_2CH$	H	Base	84–86	Et_2O	33	A	$C_{11}H_{17}NO$	7.81	7.63
CH_3O	H	H	H	Base	119–120[f]	C_6H_6	45	A	$C_9H_{13}NO_2$	8.38	8.02
H	H	CH_3O	H	Fumarate	185.5–188[g]	MeOH	41	A	$(C_9H_{13}NO_2)_2 \cdot C_4H_4O_4$	6.22	5.99
H	$C_6H_5CH_2O$	H	H	Base	110–112	C_6H_6–Et_2O	53	A	$C_{15}H_{17}NO_2$	5.76	5.54
H	CH_3O	CH_3O	H	Hydrogen Fumarate	178–180[h]	MeOH–C_6H_6	61, 72	A, B	$C_{10}H_{15}NO_3 \cdot C_4H_4O_4$	4.47	4.46
H	OCH_2O		H	Base	72.5–74.5[i]	C_6H_6	71	A	$C_9H_{11}NO_3$		
H	CH_3O	CH_3O	CH_3O	Fumarate	222–224[j]	MeOH	56, 86	A, B	$(C_{11}H_{17}NO_4)_2 \cdot C_4H_4O_4$	4.91	4.78
H	H	CH_3O_2C	H	Fumarate	184 dec.	MeOH	74.5	B	$(C_{10}H_{13}NO_3)_2 \cdot C_4H_4O_4$	4.50	4.40

[a] E. Kolshorn, *Ber.*, **37**, 2474 (1904), reports the free base has m.p. 40°. [b] J. S. Buck, *J. Am. Chem. Soc.*, **55**, 2593 (1933), reports the *p*-nitrobenzoyl derivative, m.p. 194°. [c] A. Burger and E. Hornbaker, *ibid.*, **74**, 5514 (1952), report the base, m.p. 93.5–94.5°. [d] A. Dornow and H. Theidel, *Ber.*, **88**, 1267 (1955), report the base, m.p. 115–116°. [e] Dornow and Theidel, ref. *d*, report the hydrochloride, m.p. 242–243°. [f] J. S. Buck, *J. Am. Chem. Soc.*, **55**, 2593 (1933), reports the base, m.p. 119–120°. [g] K. Kindler and W. Peschke, *Arch. Pharm.*, **269**, 581 (1931), report the free base, m.p. 70°. [h] The free base melted at 72–76°; it is reported by K. Kindler and W. Peschke, ref. *g*, to melt at 77°. [i] K. Kindler and W. Peschke, ref. *g*, report the free base, m.p. 75°. [j] A sample of the free base melted at 139–143°; it is reported by K. Kindler and W. Peschke, ref. *g*, m.p. 144°.

ing in light of the reported hydrolysis reaction of 2-amino-2-oxazoline.[10]

Hydrogenation of V over palladium on carbon in ethanol solution provided a good yield of the ring opened hydrogenolysis product (α-methylphenethyl)urea (IX).[11]

Treatment of V with methyl iodide in methanol in the presence of potassium carbonate at reflux gave about 25% of a pure monomethyl derivative, isolated as the fumarate. This compound was shown to be the known 2-imino-3,4-dimethyl-5-phenyloxazolidine (X) by preparation of an authentic sample from *dl*-ephedrine and cyanogen bromide.[4c]



Acetylation of V with acetic anhydride in pyridine led to a single product in good (70%) yield. Analyses and spectra of this compound were in agreement with monoacetylurea structures XI or XII. However, the available data did not allow us to distinguish between these two possibilities.

Structure–Activity Relationships.—Anorectic activity was determined by the compound's ability to inhibit the consumption of beef broth after oral administration in rats. Details of this method are published elsewhere.[12] Amphetamine hydrochloride shows an ED_{50} of 15.8 mg./kg. (95% confidence limits 9.5–26.2 mg./kg.) in this test while *d*-amphetamine sulfate has an ED_{50} of 6.8 mg./kg. (3.9–8.6). Thus, as can be seen in Table I, aminooxazoline V has about the same potency as racemic amphetamine while *d*-amphetamine and compound I are equipotent.

The noticeable effect of optical isomerism on anorectic activity in the case of the amphetamines prompted our examination of several isomers of 2-amino-4-methyl-5-phenyl-2-oxazoline (V). Compound V is *cis*, having been derived from the *erythro* amino alcohol *dl*-norephedrine. The diastereoisomeric *threo* isomer, *dl*-norpseudoephedrine was prepared by inversion of N-benzoylnorephedrine[13] and converted to *trans*-2-amino-4-methyl-5-phenyl-2-oxazoline (Va). However, Va proved to have a potency very similar to V. The dextrorotatory form (+Va) of Va was prepared from commercially available *d*-norpseudopehedrine[14] and surprisingly, was found to have about the same potency as V and Va. Thus, it would appear that, at least among the isomers examined, stereoisomerism plays a minor role in the anorectic activity of 2-amino-5-aryloxazolines.

Major changes in the structure of I and V all caused a loss of activity. Thus, for the fully aromatic 2-amino-5-phenyloxazole[5] (III, $ED_{50} > 30$); the parent 2-amino-2-oxazoline[2] ($ED_{50} > 30$); 2-amino-5-methyl-4-phenyl-2-oxazoline[4b,15] (II, Ar = C_6H_5, R = CH_3; $ED_{50} > 10$); the ring methylated compound X[4c] ($ED_{50} > 100$) and the 2-amino-5-phenyl-2-oxazolin-4-one[6] (IV, $ED_{50} > 30$),[16] no activity was detected at the highest doses tested.

Substitution on the 2-amino group caused a loss of activity with the exception of the 2-dimethylamino derivative XIV which showed an ED_{50} of about 7 mg./kg. Substitutions on the benzene ring of I had a profound effect on activity. Alkoxy substituents (XXIX–XXXIV) reduced anorectic activity to a very low level as did a *p*-isopropyl and *p*-carbomethoxy group XXVIII, XXXV). The 2-imino-3-methyl-5-(*m*-hydroxyphenyl)oxazolidine XXXVII (cyclization product of phenylephrine) was also relatively inactive ($ED_{50} > 10$). On the other hand, halogens substituted at the *para* position of the benzene ring augmented activity. The *p*-chloro analog XX was found to be more than twice as potent and the *p*-fluoro compound XXV about 4 times as active as I. The *p*-bromo derivative XXIV was similar to XX. Chloro substituents at the *ortho* and *meta* positions were detrimental to activity. A trifluoromethyl group at the *meta* or *para* position gave compounds with about the same activity as I.

Attempts to correlate these structure–activity findings with the nature of the substituent on the benzene ring were generally unsatisfactory. Thus, the most active compounds possess electron withdrawing groups (halogen, trifluoromethyl) at the *para* position of the benzene ring. Yet the electronically equivalent *o*-chloro compound XVIII, the sterically similar *p*-isopropyl derivative XXVIII and the sterically and electronically similar *p*-carbomethoxy compound XXXV were much less active.

As in the case of anorectic acitivity, the CNS and cardiovascular effects of these aminooxazolines were found to vary significantly with changes in structure. The results of these studies will be reported elsewhere in detail.[17]

The anorectic activity found for several of these compounds in rats has been substantiated in human beings.

Experimental[18]

Amino Alcohols.—The following amino alcohols were obtained commercially: *dl*-norephedrine from Fisher Chemical Company; *d*-norpseudoephedrine from K & K Laboratories, Inc.; phenylephrine from Specific Pharmaceuticals. The preparation of *dl*-norspeudoephedrine was accomplished by the inversion of the benzamide of *dl*-norephedrine, and is described in detail below. 2-Hydroxy-3-phenoxypropylamine was prepared by the reaction of ammonia and 1,2-epoxy-3-phenoxypropane.[19]

(10) E. Fromm, *Ann.*, **442**, 130 (1925).

(11) L. W. Jones and E. S. Wallis, *J. Am. Chem. Soc.*, **48**, 169 (1926).

(12) A. P. Roszkowski and N. M. Kelley, *The Pharmacologist*, **3**, 76 (1961).

(13) See M. Rebstock, G. W. Moersch, A. C. Moore, and J. M. Vandenbelt, *J. Am. Chem. Soc.*, **73**, 3666 (1951), for a similar inversion of N-acetylnorephedrine.

(14) Obtained from K & K Laboratories.

(15) Prepared unequivocally from phenylacetone *via* nitrosation, reduction, and cyanogen bromide ring closure due to the possible ambiguity of known methods.[4a,4b]

(16) Anorectic and CNS stimulant activity has been recently reported[6b] for derivatives of IV with alkyl substituents on the 2-amino group.

(17) J. F. Gardocki and J. Yelnosky, manuscript in preparation.

(18) Melting points are corrected. Infrared spectra were obtained on a Perkin–Elmer Model 21 or 37 spectrometer and ultraviolet spectra were determined in methanol with a Cary Model 14 spectrometer.

(19) Obtained from Eastman Organic Chemicals.

Following the procedure of Boyd[20] we obtained the primary amine in 44% yield and the secondary amine in 42.5% yield.

The remainder of the amino alcohols are described in Table II and were prepared by one of the following methods for which representative procedures are given.

Method A. α-Aminomethylbenzyl Alcohol.—A solution of 42 g. (0.315 mole) of mandelonitrile[21] in 600 ml. of anhydrous ether was added dropwise to a stirred suspension of 30 g. (0.79 mole) of lithium aluminum hydride in 600 ml. of anhydrous ether at 0° over a period of 90 min. The mixture was heated at reflux for 18 hr. It was then cooled to 0° and the excess hydride destroyed by the careful addition of 60 ml. of water and 30 ml. of 20% sodium hydroxide solution. The inorganic solids were removed by filtration and washed with several portions of hot ether. The filtrate was concentrated to about one third of its original volume under reduced pressure, and white plates precipitated. The product was collected and dried: yield 25.0 g. (58%); m.p. 40–41°.[22]

Method B. Methyl *p*-(1-Hydroxy-2-nitroethyl)benzoate.—A solution of 16.0 g. (0.098 mole) of methyl *p*-formylbenzoate[23] in 60 ml. of absolute ethanol was added to a solution of 5.23 ml. (0.098 mole) of nitromethane and 0.098 mole of sodium methoxide in 60 ml. of absolute methanol. The mixture was stirred at 0° for 2 hr., and 800 ml. of absolute ether was added. The finely divided white solid which precipitated was collected by filtration and suspended in 400 ml. of absolute ether. Glacial acetic acid (6.0 g., 0.10 mole) was added and the mixture was stoppered and placed in the refrigerator overnight. The solid was removed by filtration and the filtrate was concentrated to dryness under reduced pressure. The resulting oil crystallized when triturated with hexane. It was recrystallized from hexane–ether; yield, 16.4 g. (73%); m.p. 78–79°.

Anal. Calcd. for $C_{10}H_{11}NO_5$: N, 6.22. Found: N, 6.32.

Methyl *p*-(2-Amino-1-hydroxyethyl)benzoate Fumarate.—A solution of 16.4 g. (0.073 mole) of methyl *p*-(1-hydroxy-2-nitroethyl) benzoate in 250 ml. of glacial acetic acid with one teaspoon of sponge nickel catalyst[24] was hydrogenated at 3.5 kg./cm.^{2} and room temperature for 5 hr. Approximately 3 equiv. of hydrogen was taken up. The catalyst was separated by filtration and the solvent was evaporated under reduced pressure. The green residual oil was dissolved in a hot saturated solution of 8.5 g. (0.073 mole) of fumaric acid in 2-propanol. The white solid which precipitated as the solution cooled was collected by filtration. It weighed 17.0 g. (74.5%). After recrystallization from methanol, it melted at 184° dec.: λ_{max}^{KBr} 2.95, 3.35, 5.82, 7.53 μ.

Anal. Calcd. for $C_{10}H_{13}NO_3 \cdot C_4H_4O_4$: N, 4.50. Found: N, 4.40.

The free base, obtained by treating a solution of the fumarate salt with potassium carbonate, melted at 78–80°.

***erythro*-DL-N-(β-Hydroxy-α-methylphenethyl)benzamide.**[25]—Norephedrine hydrochloride (37.6 g., 0.2 mole) was converted to its N-benzoyl derivative by a Schotten–Baumann reaction with 35 g. (0.25 mole) of benzoyl chloride and 20 g. (0.5 mole) of sodium hydroxide in 400 ml. of water. After one recrystallization from ethanol–water, there was obtained 28.6 g. (56%) of the benzamide, m.p. (128°) 145.5–147°. The literature[25] m.p. for the compound is 143°; λ_{max}^{Nujol} 2.98, 3.05, 3.30 (w), 6.10, 6.23(w), 6.32, 6.46, 7.49 μ.

Anal. Calcd. for $C_{16}H_{17}NO_2$: N, 5.49. Found: N, 5.49, 5.57.

Norpseudoephedrine.[13,26]—To 48 ml. (0.67 mole) of thionyl chloride was added in portions 10 g. (0.0392 mole) of *erythro*-*dl*-N-(β-hydroxy-α-methylphenethyl)benzamide. The resultant clear solution was warmed for 2.5 hr. at 50–60°, then poured slowly with swirling into ice. The aqueous mixture was refluxed for 1 hr., affording a thick white solid, identified as O-benzoylnorpseudoephedrine hydrochloride. Ethanol (100 ml.) was added to afford solution and the solution was heated under reflux for 90 hr. and then was concentrated *in vacuo* to remove the alcohol. The aqueous solution was cooled and benzoic acid was removed by filtration, m.p. 119–124°. The acidic filtrate was made strongly basic with concd. sodium hydroxide and extracted 3 times with methylene chloride. The extracts were dried over potassium carbonate and concentrated at reduced pressure, yielding 5.25 g. (89%), m.p. 70–72°. The literature[26] m.p. is 71°.

2-Amino-2-oxazolines. Method A. 2-Amino-5-phenyl-2-oxazoline (I).—A solution of 15.5 g. (0.146 mole) of cyanogen bromide[19] in 50 ml. of methanol was added over a period of 15 min. to a solution of 20.0 g. (0.146 mole) of α-aminomethylbenzyl alcohol and 24.0 g. (0.292 mole) of sodium acetate in 300 ml. of methanol at 0°. The solution was stirred at 0° for 45 min. The solvent was evaporated under reduced pressure and the oily residue was dissolved in water. A concentrated solution of potassium carbonate was added and a white solid precipitated. It was collected by filtration, washed, dried and recrystallized from benzene: yield, 15.0 g. (63%), m.p. 135–136°: $\lambda_{max}^{CHCl_3}$ 2.95, 5.95, 6.30, 7.13 μ: ultraviolet: phenyl end absorption.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.90; H, 6.32; N, 17.08.

2-Imino-3-methyl-5-(*m*-hydroxyphenyl)oxazolidine (XXXVII).—Phenylephrine hydrochloride (16.8 g., 0.083 mole) was dissolved in the minimum amount of water and concentrated ammonia was added. The free base precipitated, and after crystallization was complete (*ca.* 1 hr.), it was removed by filtration, washed and dried: yield 10.28 g. (74%), m.p. 172–174°. The free phenylephrine (10.3 g., 0.0615 mole) and 21.2 g. (0.25 mole) of sodium acetate were suspended in 150 ml. of methanol. The mixture was cooled to 0° and a solution of 6.6 g. (0.063 mole) of cyanogen bromide in 40 ml. of methanol was added. The reaction mixture became homogeneous and was stirred for 3 hr. The solvent was evaporated under reduced pressure. Concentrated ammonia solution was added and white crystals precipitated. They were collected by filtration, dried and weighed 7.7 g. (73%). Recrystallization twice from 2-propanol gave 6.3 g. of crystals melting at 179–182°: λ_{max}^{KBr} 3.01, 6.02, 6.28, 7.78, 9.81 μ; λ_{max} 278 mμ (ε 2030).

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29. Found: C, 62.53; H, 6.21.

Method B. 1-Methyl-3-(β-hydroxy-α-methylphenethyl)urea.—An aqueous solution of norephedrine hydrochloride was made basic with sodium hydroxide. The precipitated norephedrine was extracted into chloroform and dried over magnesium sulfate. The chloroform was evaporated under reduced pressure leaving crystalline norephedrine, m.p. 100–102°. A solution of 15.1 g. (0.10 mole) of norephedrine in 200 ml. of methylene chloride was cooled to 0°. A solution of 5.7 g. (0.10 mole) of methyl isocyanate in 10 ml. of methylene chloride was added to the stirred solution of norephedrine. The reaction mixture was stirred for 2 hr. It was extracted with a dilute aqueous solution of sodium dihydrogen citrate. The methylene chloride solution was dried over sodium sulfate, and the solvent was evaporated under reduced pressure leaving 13.5 g. (65%) of a clear oil which could not be induced to crystallize. λ_{max}^{Nujol} 3.00, 6.17, 6.40, 7.95, 10.01 μ.

2-Methylamino-4-methyl-5-phenyl-2-oxazoline (XIII).—A solution of 10.5 g. (0.050 mole) of 1-methyl-3-(β-hydroxy-α-methylphenethyl)urea in 200 ml. of methylene chloride was cooled to 0°. A solution of 5.5 g. (0.050 mole) of thionyl chloride in 20 ml. of methylene chloride was added. The mixture was heated at the reflux temperature for 30 min. A yellow solid precipitated. The solvent was evaporated under reduced pressure leaving a yellow semisolid. The residue was dissolved in boiling water. The aqueous solution was filtered, cooled, and made basic by addition of a concentrated potassium carbonate solution. The oil which separated was extracted into methylene chloride, and dried over sodium sulfate. The solvent was evaporated under reduced pressure leaving 7.9 g. (83%) of a solid which melted at 122–126°. After two recrystallizations from benzene–hexane, crystals melting at 129–131° were obtained. λ_{max}^{KBr} 3.15, 3.40, 5.95, 6.05, 6.35, 10.00, 14.35 μ.

1-Hydroxyimino-1-phenyl-2-propanone.[27a,b]—Phenylacetone (67.0 g., 0.5 mole) was nitrosated in sodium ethoxide solution with butyl nitrite essentially by the procedure of Kolb.[27a] After recrystallization from ether–petroleum ether 47.4 g. (58%) of product was obtained, m.p. 166–170°. Literature[27b] m.p. 165°; λ_{max}^{KBr} 3.10, 6.00, 7.03, 7.32 μ: λ_{max} 222 mμ (ε 11,250): λ_{shl} 252 mμ (ε 4850).

Anal. Calcd. for $C_9H_9NO_2$: N, 8.58. Found: N, 8.32.

(20) D. R. Boyd, *J. Chem. Soc.*, **97**, 1791 (1910).

(21) O. Wallach, *Ann.*, **193**, 1 (1878); prepared by the method of J. Levine, T. E. Eble, and H. Fishback, *J. Am. Chem. Soc.*, **70**, 1930 (1948).

(22) Reported m.p. 40°; E. Kolschorn, *Ber.*, **37**, 2474 (1904).

(23) H. Simmonis, *Ber.*, **45**, 1584 (1912).

(24) Davison Chemical Co.

(25) S. Kanao, *J. Pharm. Soc. Japan*, **48**, 1070 (1928).

(26) W. N. Nagai and S. Kanao, *Ann.*, **470**, 157 (1929).

(27) (a) A. Kolb, *Ann.*, **291**, 253 (1896); (b) W. Borsche, *Ber.*, **40**, 737 (1907).

β-Amino-α-methylphenethyl Alcohol.[28]—Hydrogenation of a 5 g. sample of 1-hydroxyimino-1-phenyl-2-propanone over 0.4 g. of platinum dioxide in methanol on a Paar shaker afforded 3.6 g. (80%) of the amino alcohol. Recrystallization of a sample from methylene chloride–ether afforded a sample melting at 76–80°, lit.,[28] m.p., 85°.

2-Amino-5-methyl-4-phenyl-2-oxazoline.[4b]—A 9 g. (0.0595 mole) sample of β-amino-α-methylphenethyl alcohol was cyclized with cyanogen bromide as described in method A. After two recrystallizations from benzene, 4.1 g. (39%) of pure oxazoline was obtained, m.p. 154–156.5°; literature m.p.,[4b] 159°; λ_{max}^{KBr} 3.03, 3.21, shl 5.90, 5.99, 6.19, 6.32, 6.69, 6.86, 7.02, 7.23 μ.

Anal. Calcd. for $C_{10}H_{12}N_2O$: N, 15.90. Found: N, 15.67, 15.71.

When V and Va were mix-melted with 2-amino-5-methyl-4-phenyl-2-oxazoline, their melting points were depressed 20°. The infrared spectra of the three compounds were also different.

Acid Hydrolysis of 2-Amino-5-phenyl-2-oxazoline (I).—A 5.0 g. sample (0.03 mole) of 2-amino-5-phenyl-2-oxazoline (I) was refluxed for 2 hr. in 310 ml. of 0.1 *N* hydrochloric acid. The solution was concentrated *in vacuo* and dried. The gummy product was washed once with ether and once with methylene chloride. The washes yielded 1.02 g. (18.8%) of (β-hydroxyphenethyl) urea (VII), m.p. 84–89° dec.; λ_{max}^{Nujol} 2.9, 3.0, 3.4, 3.5, 6.12, 6.24, 6.4, 6.75, 6.85, 6.92 μ. The gummy product crystallized from methylene chloride and was recrystallized from absolute ethanol–ether, affording 3.75 g. (56%) of VII hydrochloride. After a second recrystallization from absolute ethanol–ether, 2.8 g. of the salt was obtained, m.p. 130–132°. A 1.0 g. sample of VII hydrochloride was converted to the free base by pouring it over a column of 15 g. of strongly basic ion exchange resin.[29] After one recrystallization from acetone–ether, 0.76 g. (91.8%) of VII was obtained, m.p. 92–94°; literature m.p. 95° (see below). λ_{max}^{KBr} 2.92, 3.05 (br), 6.10, 6.20, 6.37, 6.68, 6.87 μ; identical with the spectrum of authentic VII.

β-Hydroxyphenethylurea (VII).[8]—The reaction of α-aminomethylbenzyl alcohol hydrochloride and potassium cyanate afforded 94.5% of crude VII. Recrystallization first from ethyl acetate and then from dilute ammonia gave VII, m.p. 93–95°; literature[8] m.p. 95°; λ_{max}^{KBr} 2.95, 3.05, 6.13, 6.24, 6.40, 6.70, 6.89 μ; λ_{max} 246 mμ. (ε 140), 252 mμ. (ε 174), 257 mμ. (ε 215), 263 mμ (ε 167).

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 60.08; H, 6.70; N, 15.64.

Hydrolysis of 2-Amino-5-phenyl-2-oxazoline (I) in Water.—A solution of 5.50 g. of 2-amino-5-phenyl-2-oxazoline in 200 ml. of water was heated with stirring at the reflux temperature for 4–5 hr. An odor of ammonia was detected. The aqueous solution was extracted 5 times with chloroform. The chloroform solution was dried over magnesium sulfate and the solvent was evaporated under reduced pressure. Approximately 0.5 g. of an oil remained which crystallized upon standing. The crystals were triturated with *N* hydrochloric acid and collected by filtration: yield 0.20 g. (3.6%); melting at 87–87.5° after one recrystallization from ethanol–hexane. It was identical by melting point, mixture melting point and infrared spectrum with authentic 5-phenyl-2-oxazolidinone (VIII) (see below); λ_{max}^{KBr} 3.07, 5.81, 6.70, 6.95, 7.30 μ.

The aqueous solution was evaporated to dryness under reduced pressure. An oil remained which crystallized when triturated with ether. There was obtained 4.2 g. (68%) of (β-hydroxyphenethyl)urea (VII) melting at 86–90°. After one recrystallization from acetone–ether, it melted at 90–92°. It was identical with the authentic sample by melting point, mixture melting point and infrared spectrum; λ_{max}^{KBr} 2.95, 3.05, 6.14, 6.24, 6.40, 6.70, 6.89 μ.

5-Phenyl-2-oxazolidinone (VIII).[9]—A 25.0 g. (0.138 mole) sample of α-aminomethylbenzyl alcohol acetate was treated with 27.4 g. (0.276 mole) of phosgene and 22.6 g. (0.276 mole) of sodium acetate in ethyl acetate. The crude product was recrystallized from methylene chloride–ether, affording 19.8 g. (88%) of VIII, m.p. 88.5–89.5°. Literature[9] m.p. 89–90°; λ_{max}^{KBr} 3.07, 5.80, 6.68, 6.90 (br), 7.30 μ.

Anal. Calcd. for $C_9H_9NO_2$: N, 8.58. Found: N, 8.52.

Attempted Acid Hydrolysis of *dl-cis*-2-Amino-4-methyl-5-phenyl-2-oxazoline (V).—A 2.0 g. sample (0.011 mole) of *dl-cis*-2-amino-4-methyl-5-phenyl-2-oxazoline (V) was dissolved in 50 ml. of *N* hydrochloric acid and refluxed for 4 hr. The solution was cooled, washed with ether and made basic with sodium hydroxide solution. The solid was filtered, washed twice with water and dried, giving 1.0 g. of V, m.p. 151–153°. Extraction of the aqueous solution afforded an additional 0.56 g. of less pure V, m.p. 133–138°, identical with V by its infrared spectrum. The total recovery was 78%.

Attempted Alkaline Hydrolysis of *dl-cis*-2-Amino-4-methyl-5-phenyl-2-oxazoline (V).—A 2.0 g. sample (0.011 mole) of *dl-cis*-2-amino-4-methyl-5-phenyl-2-oxazoline (V) was dissolved in 25 ml. of ethanol and 50 ml. of dilute sodium hydroxide (0.15 mole) and refluxed for 4 hr. The ethanol was removed by distillation and the gummy solid extracted into ether. The organic solution was extracted 3 times with dilute hydrochloric acid, which was made basic and extracted with methylene chloride. The solution was dried and concentrated, yielding 1.1 g. (55%) of V. After recrystallization from benzene, 0.82 g. of V was obtained, m.p. 145–152°, identified by infrared spectra.

Treatment of *dl-cis*-2-Amino-4-methyl-5-phenyl-2-oxazoline (V) with Nitrous Acid.—To 2 g. (0.011 mole) of *dl-cis*-2-amino-4-methyl-5-phenyl-2-oxazoline (*V*), dissolved in 15 ml. of water and 1.3 ml. (0.023 mole) of concd. sulfuric acid and cooled in an ice-water bath, was added slowly a solution of 1.6 g. (0.023 mole) of sodium nitrite in 10 ml. of water. After stirring at 0° for 1.5 hr., the solid product was filtered, washed with water and sucked dry, yielding 0.94 g. (34.7%) of V nitrate, m.p. 154–156.5°. A 0.085 g. sample was recrystallized from methanol–benzene, yielding 0.08 g. of the salt, m.p. 154–156°; λ_{max}^{Nujol} 3.12, 3.27, 3.46, 3.53, 5.82, 6.20, 6.57, 6.90, 7.15, 7.26 μ.

Anal. Calcd. for $C_{10}H_{13}N_3O_4$: C, 50.20; H, 5.48; N, 17.57. Found: C, 49.91; H, 5.47; N, 17.49.

The authentic nitrate was prepared from V and nitric acid and was identical in all respects to this salt.

The aqueous mother liquor from the nitrous acid reaction was made basic with sodium hydroxide and the solid product filtered, washed with water and sucked dry, yielding 1.04 g. (52%) of V, m.p. 154–156.5°; identified by infrared spectra.

Hydrogenolysis of *dl-cis*-2-Amino-4-methyl-5-phenyl-2-oxazoline (V).—A solution of 1.50 g. (0.010 mole) of *dl-cis*-2-amino-4-methyl-5-phenyl-2-oxazoline (V) in 30 ml. of methanol containing 0.15 g. of 10% palladium on charcoal in suspension was hydrogenated at room temperature and atmospheric pressure. The uptake of hydrogen was complete in 2 hr. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. White crystals, m.p. 151–152°, were obtained; yield 1.50 g. (98%). This material was identical by melting point, mixture melting point and infrared spectrum with authentic α-methylphenethylurea (IX) prepared by the method of Jones and Wallis.[11]

Methylation of *dl-cis*-2-Amino-4-methyl-5-phenyl-2-oxazoline.—To 2 g. (0.011 mole) of *dl-cis*-2-amino-4-methyl-5-phenyl-2-oxazoline (V) in 35 ml. of methanol was added 4.7 g. (0.034 mole) of potassium carbonate and 4.85 g. (0.034 mole) of methyl iodide. The mixture was heated under reflux for 5 hr., diluted with water and concentrated to remove the alcohol. The solid product was filtered, dissolved in ether and extracted into dilute hydrochloric acid. The acid solution was made basic and extracted 3 times with methylene chloride. The extracts were dried over magnesium sulfate and concentrated, yielding 2.0 g. of basic product. Crystallization of the material from benzene–petroleum ether afforded 0.65 g. (32%) of unchanged V, m.p. 153.5–156°, identified by infrared spectra.

The mother liquor, 0.8 g. (40%), was dissolved in methanol and treated with 0.4 g. of fumaric acid. After dilution with ether, crystallization occurred. The crystals were filtered, washed with ether and dried, giving 0.5 g. of 2-imino-3,4-dimethyl-5-phenyloxazolidine (X) fumarate, m.p. 173–178° dec. After one recrystallization from methanol-ether, an analytical sample was obtained, m.p. 171.5–175°; λ_{max}^{KBr} 3.35 (br), 5.85, 6.20, 6.57, 6.86, 7.0 μ.

Anal. Calcd. for $C_{15}H_{18}N_2O_5$: C, 58.81; H, 5.92; N, 9.15. Found: C, 58.94; H, 6.02; N, 9.12.

A 0.15 g. sample of X fumarate was dissolved in water and the solution was made basic with 5% sodium hydroxide and extracted 3 times with ether. The extracts were washed with water, dried and concentrated. Trituration of the solid product with petroleum ether afforded 0.04 g. of X, m.p. 68–71°; λ_{max}^{KBr} 3.00, 3.35, 3.48, 5.99, 6.45, 6.66, 6.89, 7.02, 7.19, 7.27, 7.37 μ. The material is identical with an authentic sample described below by melting point, mixture melting point and infrared spectra.

Anal. Calcd. for $C_{11}H_{14}N_2O$: N, 14.73. Found: N, 14.74.

(28) J. Sicher and M. Pánková, *Collection Czech. Chem. Commun.*, **20**, 1409 (1955).

(29) IRA-400, Rohm and Haas.

2-Imino-3,4-dimethyl-5-phenyloxazolidine (X).[40]—A 7.0 g. sample (0.0425 mole) of *dl*-ephedrine[30] was cyclized with cyanogen bromide using Method A. After recrystallization from ether–petroleum ether, 4.77 g. (59.5%) of pure 2-imino-3,4-dimethyl-5-phenyl-2-oxazolidine (X) was obtained, m.p. 67–71°. Literature[40] m.p. 71–73°; λ_{max}^{KBr} 3.0, 3.35, 3.47, 5.95, 6.45, 6.65, 6.88, 7.02, 7.17, 7.27, 7.35 μ.

1-(or 3-)Acetyl-1-(β-hydroxy-α-methylphenethyl)urea (XI or XII).—To a solution of 5 g. (0.0286 mole) of 2-amino-4-methyl-5-phenyl-2-oxazoline (V) in 65 ml. of pyridine was added 8 ml. of acetic anhydride. The solution was left to stand at room temperature for 72 hr.; it was then acidified with cold 10% hydrochloric acid and washed 3 times with ether. The aqueous solution was made basic with 30% sodium hydroxide solution and extracted thoroughly with ether and methylene chloride. The extracts were dried and concentrated, affording 3.3 g. of product. The aqueous basic solution was saturated with salt and re-extracted, affording an additional gram of product. The two crops were combined and recrystallized from methanol–benzene, yielding 3.2 g. (51.5%) of the substituted urea: m.p. (198.5) 208.5–211.5° dec. The sample was recrystallized once from methanol–benzene and once from acetone affording 1.77 g. of product, m.p. 206–207.5°; λ_{max}^{KBr} 2.94, 3.02, 3.15, 3.35, 5.86, 6.10, 6.40, 6.66, 6.86, 6.96, 7.17, 7.25 μ.

Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.12; H, 6.90; N, 11.91.

(30) Obtained from Merck and Co., Inc.

Hypotensive 1,2,4-Benzothiadiazines

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2-Aminobenzenesulfonamides were prepared by way of (1) the chlorosulfonation of aminobenzenes, (2) the amination of 2-chlorobenzenesulfonamides and (3) the chlorine oxidation of 2-benzylmercaptonitrobenzenes. New 1,2,4-benzothiadiazine-1,1-dioxides were obtained by the cyclization of the 2-aminobenzenesulfonamides with formic acid, ortho esters, mixed anhydrides and with aldehydes. The hypotensive activities of the endocyclic sulfonamides are described.

Since the hypotensive activity of 6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide was recognized clinically,[1] there has been a search in this laboratory for sulfonamides having principally or exclusively effective hypotensive activity. This paper describes part of the investigation concerned with 1,2,4-benzothiadiazine-1,1-dioxides not containing an extranuclear 7-sulfamoyl group.

Chlorosulfonation of 3-chloro-4-methylaniline and of 4-chlorobenzoic acid yielded, respectively, 2-amino-4-chloro-5-methylbenzenesulfonyl chloride and 5-carboxy-2-chlorobenzenesulfonyl chloride. The reactive chlorine atoms of 2,3-dichloronitrobenzene and of 2-chloro-5-methylnitrobenzene were displaced by benzylthiol in alkaline solution. Chlorine oxidation of the resulting 2-benzylmercapto-3-chloronitrobenzene and 2-benzylmercapto-5-methylnitrobenzene yielded the corresponding 2-nitrobenzenesulfonyl chloride. All the above sulfonyl chlorides were converted to sulfonamides by treating them with liquid ammonia. Reactions of 5-chloro-2-nitrobenzenesulfonyl chloride with *n*-propylamine and with benzylamine yielded N-*n*-propyl- and N-benzyl-5-chloro-2-nitrobenzenesulfonamides. Catalytic reduction of the 2-nitrobenzenesulfonamides and displacement of the chlorine of 2-chloro-5-carboxybenzenesulfonamide yielded the 2-aminobenzenesulfonamides listed in Table I.

Cyclization of 2-aminobenzenesulfonamides with formic acid, triethyl orthoformate, triethyl orthoacetate and with triethyl orthopropionate yielded 3-H-, 3-methyl- and 3-ethyl-1,2,4-benzothiadazine-1,1-dioxides (Table II). Mixed anhydrides of trifluoroacetic acid with alkane, aralkane and cycloalkanecarboxylic acids reacted with the 2-aminobenzenesulfonamides to give 2-carboxamidobenzenesulfonamides. One of these, 5-chloro-2-phenacetylaminobenzenesulfonamide, was isolated and characterized. The other crude 2-carboxamidobenzenesulfonamides were cyclized in concentrated ammonium hydroxide to yield 3-alkyl (4 or more carbons), 3-aralkyl- and 3-cycloalkyl-1,2,4-benzothiadiazine-1,1-dioxides (Table II). The mixed anhydride method was not successful with benzoic acid, and 6-methyl-3-trifluoromethyl-1,2,4-benzothiadiazine-1,1-dioxide was obtained from the reaction with the anhydride of trifluoroacetic acid and 3,4,5-trimethoxybenzoic acid. Condensations of aldehydes with the 2-aminobenzenesulfonamides in acid gave the 2,3-dihydro-3-alkyl-, aralkyl- and cycloalkyl-1,2,4-benzothiadiazine-1,1-dioxides (Table III). The unusual and new adamantane-1-carboxaldehyde was prepared by the lithium aluminum hydride reduction of N-methyl-N-phenyl-adamantane-1-carboxamide. This amide was obtained from adamantane-1-carboxylic acid through the acid chloride.

Experimental

Chlorosulfonations (Table I).—To 1 kg. of chlorosulfonic acid was added carefully 100 g. of 3-chloro-4-methylaniline or 100 g. of *p*-chlorobenzoic acid. The mixture was stirred mechanically, and 150–200 g. of NaCl was added in small portions. The escaping hydrogen chloride was conducted to a water-wash column. The reaction mixture was heated in an oil-bath at 160° for 5 hr., then cooled and added to ice water. The separated sulfonyl chloride was extracted with ether or collected on a filter, washed with water and dried. The product was added cautiously to excess liquid ammonia in an open beaker. After the excess ammonia had evaporated, the solid sulfonamide was recrystallized from alcohol.

2-Benzylmercaptonitrobenzenes and their Chlorine Oxidation (Table I).—To a cold solution of KOH (54–108 g.) in 2 l. of alcohol was added 100 g. of benzylmercaptan and either 154.5 g. of 2,3-dichloronitrobenzene or 128 g. of 2-chloro-5-methylnitro-

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