

- (11) H. G. Richey, Jr., and F. W. Von Rein, *Tetrahedron Lett.*, 3781 (1971).
 (12) T. R. Hopkins, R. P. Neighbors, P. D. Strickler, and L. S. Phillips, *J. Org. Chem.*, **24**, 2040 (1959).

- (13) T. R. Hopkins, J. H. Rea, P. D. Strickler, and W. Vanderlinde, *ibid.*, **27**, 659 (1962).
 (14) F. F. Vincenzi and T. C. West, *J. Pharmacol. Exp. Ther.*, **150**, 349 (1965).

Some 2-Amino-5-substituted Oxazolines and Intermediates as Potential Anorectants

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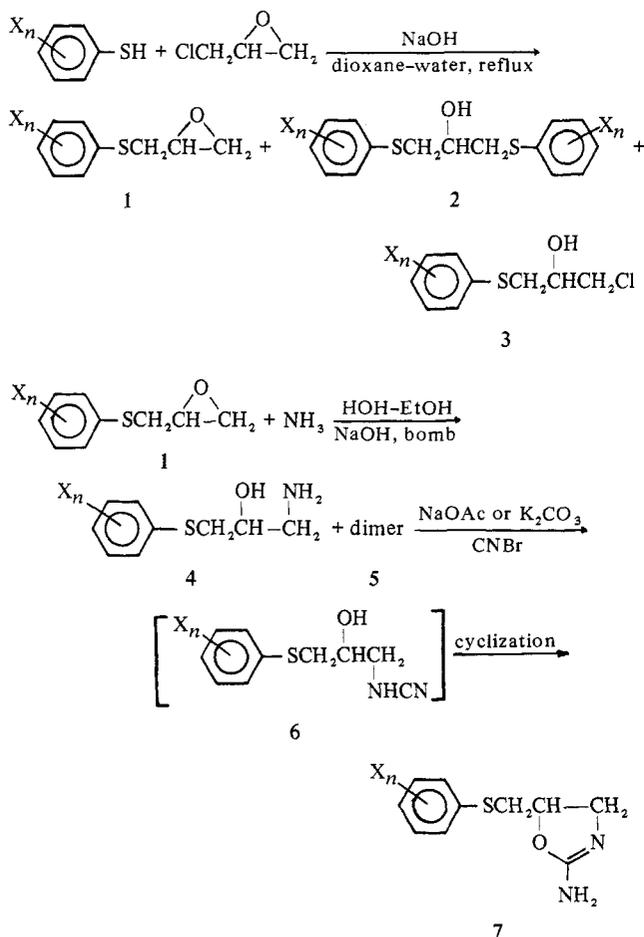
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The synthesis of some 2-amino-5-arylthiomethylloxazolines and intermediates is reported. These compounds and some of their intermediates although less active than *d*-amphetamine were found to have significant anorectant activity. The most active in this series was found to be 2-amino-5-(phenylthiomethyl)oxazoline (7a) and caused a significant decrease in the food intake of male albino rats when compared to controls.

The search for anorectants has covered a wide range of chemical structures including numerous heterocyclic ring systems.¹ Poos, *et al.*,² have previously synthesized a series of 2-amino-5-phenyloxazolines which have exhibited anorectant and CNS activity. The work reported here differs from the above in that the 5 position on the 2-aminoxazolines is substituted by various arylthiomethyl derivatives. These compounds along with the 1-amino-3-arylthio-2-propanol intermediates have exhibited significant anorectant activity.

Chemistry. The route by which the oxazolines and amino alcohols were synthesized is shown in Scheme I. The reaction of epichlorohydrin with mercaptans is documented in the literature^{3,4} and proceeds as illustrated in Scheme I. In our hands it was found that the desired epoxide **1** could

Scheme I



be formed free of the dimer **2** and the chlorohydrin **3** by a slight modification of previously reported experimental conditions. The reaction mixture was changed to include a large excess of epichlorohydrin and a slight excess or equivalent of NaOH (see Experimental Section). The epoxide **1** although stable at room temperature had a tendency to decompose at higher temperatures. Decomposition was quite evident when running vpc and was also obvious during distillation.

There are several literature references pertaining to the opening of epoxides with amines.⁵⁻⁷ It was found that good yields of 1-amino-3-thioaryl-2-propanol (**4**) could be obtained (with negligible amounts of dimer) by using a large excess of NH₃ in water with a trace of NaOH as catalyst.

The final step in the synthesis was formation of the oxazoline ring by treatment of the amino alcohol **4** with cyanogen bromide^{2,8} in the presence of an acid acceptor. The reaction proceeded through an intermediate (probably the corresponding hydroxycyanamide, **6**). This intermediate did not cyclize spontaneously as previously reported² and could be detected by following the reaction on tlc. Attempts to isolate this open-chain intermediate by removing the solvent under vacuum, however, were unsuccessful and resulted only in the isolation of end product **7**.

Biological Activity and Discussion. Table I shows that the substitution of 4-chloro (**7b**) and 3,4-dichloro (**7c**) on the phenyl ring caused a decrease in the oral and intraperitoneal acute toxicities of the phenylthiooxazolines. On the other hand, the 4-methoxy substitution (**7d**) increased toxicity. However, in the case of the open-ring intermediates, the 3,4-dichloro (**4c**) was more toxic than either the 4-chloro (**4b**) or the unsubstituted (**4a**) compound.

All compounds tested caused some degree of anorexia in mice. When compared on a milligram per kilogram basis their anorectant activity was less than that of *d*-amphetamine or of the related compound 2-amino-5-phenyloxazoline (aminorex).² The 46 mg/kg doses of compounds **7a-d** caused significant (*p* < 0.05) reduction of food intake only at the 1-hr interval. Our results show that the halogenation of the phenyl ring in the 4 or 3,4 positions decreased acute toxicity without significantly reducing anorectant activity. In equipotent anorectant doses with *d*-amphetamine, the oxazolines **7a-d** caused moderate increases in spontaneous motor activity which was less than that of *d*-amphetamine.

Experimental Section

Pharmacology. Groups of three male, albino mice (25-30 g) (Harlan Industries, Cumberland, Ind.) were placed in suspended

Table I

Compd	Ar	Method of preparation	% yield	Mp, °C	Formula	LD ₅₀ , mg/kg		Dose, mg/kg po	Anorectic activity, % reduction in food intake	
						ip	po		1 hr	6 hr
<i>d</i> -Amphetamine						25	40	2.1	59 ^a	0.0
Aminorex					C ₉ H ₁₁ N ₂ O	21.5		4.6	74 ^a	0.0
7a	C ₆ H ₅ -	B	88	111-112	C ₁₀ H ₁₂ N ₂ OS	178	147	21	9	4
7b	<i>p</i> -Cl-C ₆ H ₄ -	B	86	136-138	C ₁₀ H ₁₁ ClN ₂ OS	215	383	21	18	3
7c	3,4-di-ClC ₆ H ₃ -	B	54	97-99	C ₁₀ H ₁₀ Cl ₂ N ₂ OS	383	562	46	45 ^a	2
7d	<i>p</i> -CH ₃ OC ₆ H ₄ -	B	72	124-125	C ₁₁ H ₁₄ N ₂ O ₂ S	56.2		46	33	11
4a	C ₆ H ₅ -	A	77	105-107	C ₉ H ₁₃ NOS	316		21	51 ^a	26
4b	<i>p</i> -Cl-C ₆ H ₄ -	A	85	109-110	C ₉ H ₁₂ ClNOS	316		21	28	0.0
4c	3,4-di-ClC ₆ H ₃ -	A	86	94-95	C ₉ H ₁₁ Cl ₂ NOS	147		46	43 ^a	17
4d	<i>p</i> -CH ₃ OC ₆ H ₄ -	A	84	96-98	C ₁₀ H ₁₅ NO ₂ S			60	A ^b	NA ^c
								60	A	NA

^aSignificantly different from control ($p < 0.05$). ^bA = active. ^cNA = not active.

wire cages (10 × 25 × 13 cm) and trained for 5 days to eat their daily meal which consisted of ground Wayne Lab Chow meal in spill-proof containers in 6 hr during the day and starved (water *ad lib*) for the remaining 18 hr. On the sixth day, compounds to be tested were administered orally; one group of mice received an equivalent volume of methylcellulose and served as a control. After drug administration (30 min), mice were allowed access to food, and food consumption by each group was measured at 1- and 6-hr intervals and compared to the amount of food consumed by the control group. Compounds were dissolved in 0.5% methylcellulose 0.5 hr before administration. Food intake was recorded in grams. The percentage reduction of food intake was calculated by comparing food intake of the drug-treated group to that of the control group. Results were analyzed by Student's *t* test; $p < 0.05$ was chosen to be the significant level in this experiment. ED₅₀'s were calculated according to the method of Litchfield-Wilcoxon.⁹ Reduction of food intake by 40% or more was considered a positive response.

Acute toxicity was determined by injecting male, albino mice with different doses of the drug intraperitoneally or by oral administration. The number of mice that died within 48 hr was recorded. LD₅₀'s were determined according to the method of Litchfield-Wilcoxon.⁹

Chemistry. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. All analytical samples had ir and nmr spectra in agreement with their assigned structure. Ir spectra were determined with a Perkin-Elmer Model 137-G Infracord grating spectrophotometer; nmr spectra were recorded on a Varian A-60 spectrometer (Me₄Si). Analyses were within 0.4% limit of the theoretical values and were performed by the Analytical Laboratories of The Dow Chemical Company, Midland, Mich. Vpc analyses were performed on a F & M research chromatograph Model 810-19 employing a 0.25 in. × 5 ft silicone-gum Chromosorb column. Mass spectra were determined on a Mass II (rebuilt Westinghouse) spectrometer.

Reaction of Thiophenol with Epichlorohydrin. Isolation and Separation of a Mixture of Compounds 1-3 (X_n = H). To 57 ml of dioxane in which was dissolved 15 g (0.136 mol) of thiophenol and 11.3 g (0.2 mol) of epichlorohydrin was added 14 ml of H₂O containing 6.4 g (0.16 mol) of NaOH. After the reaction had subsided the mixture was heated on a steam bath at gentle reflux for 6 hr. The NaCl which formed was filtered off. The two-layered reaction mixture was left in the refrigerator overnight and then extracted twice with benzene. The benzene layer was dried (MgSO₄), filtered, and evaporated *in vacuo* leaving a clear liquid residue which exhibited three components on vpc. The liquid residue was distilled under reduced pressure to yield three fractions: 3.0 g (13%) of 1-phenylthio-2,3-epoxypropane (1) [bp 85-90° (0.3-0.5 mm); *n*²⁵_D 1.5790; *m/e* 166. *Anal.* (C₉H₁₀OS) C, H, S], 6.1 g (16%) of 1,3-di-

phenylthio-2,3-epoxypropane (2) [bp 195° (0.25 mm); *n*²⁵_D 1.6308; *m/e* 276. *Anal.* (C₉H₁₀OS) C, H, S], and 1.2 g (4%) of impure 1-phenylthio-2-hydroxy-3-chloropropane (3) [bp 100-105° (0.3-0.5 mm); *n*²⁵_D 1.6008; *m/e* 202]. A residue remained which was discarded.

1-Arylthio-2,3-epoxypropanes (1). To 375 ml of anhydrous EtOH in which had been dissolved 10.92 g (0.273 mol) of NaOH was added with stirring 0.273 mol of aryl mercaptan. The resulting solution was added over a period of 1 hr to 70 g (0.757 mol) of epichlorohydrin dissolved in a mixture of 300 ml of dioxane and 75 ml of H₂O at a temperature of 75-80°. After addition was complete the reaction mixture was held at a temperature of 70° for 5 min and then cooled in an ice bath to ca. 10°. The NaCl which formed was filtered off and the filtrate was concentrated *in vacuo*. The remaining liquid was dissolved in CH₂Cl₂, washed with H₂O, dried (MgSO₄), and concentrated *in vacuo*. The remaining liquid was distilled under reduced pressure to yield the corresponding 1-arylthio-2,3-epoxypropane.

The 1-arylthio-2,3-epoxypropanes (1) synthesized by the above method were: 1-(phenylthio)-2,3-epoxypropane, bp 85-90° (0.3 mm) [lit.¹⁰ bp 131.2° (6 mm)], *n*²⁵_D 1.5775, 65% [*Anal.* (C₉H₁₀OS) C, H, S]; 1-(4-chlorophenylthio)-2,3-epoxypropane, bp 100° (0.3 mm) [lit.¹⁰ bp 158-162° (3 mm)], *n*²⁵_D 1.5893, 86% [*Anal.* (C₉H₉ClOS) C, H, S]; 1-(3,4-dichlorophenylthio)-2,3-epoxypropane, bp 140° (1.0 mm), *n*²⁵_D 1.6055, 80% [*Anal.* (C₉H₈Cl₂OS) C, H, S]; 1-(4-methoxyphenylthio)-2,3-epoxypropane, bp 127° (0.5 mm), *n*²⁵_D 1.5725, 71% [*Anal.* (C₁₀H₁₂O₂S) C, H, S].

Method A. 2-Hydroxy-3-arylthiopropylamines (4a-d) (Table I). To 100 ml of EtOH in a 300-ml bomb containing one pellet of NaOH and 5 g of 1-arylthio-2,3-epoxypropane was added 100 ml of enriched NH₄OH solution (the NH₄OH solution had been enriched by bubbling NH₃ into 85 ml of 28% NH₄OH, cooled in an ice bath, until the total volume reached 100 ml). The bomb was sealed and shaken at 25° for 10-12 hr. The bomb was dismantled and the reaction mixture was concentrated to dryness by subjecting it to an air stream for ca. 12 hr. The solid remaining was dissolved in hot chlorobenzene and filtered. The pure compound crystallized on cooling. *Anal.* C, H, N.

Method B. 2-Amino-5-arylthiomethyl-2-oxazolines (7a-d) (Table I). To 20 ml of CH₃OH containing 0.00546 mol of 2-hydroxy-3-arylthiopropylamine 1 g (0.0122 mol) of NaOAc was added dropwise with stirring and 0.6 g (0.0057 mol) of CNBr dissolved in 83 ml of CH₃OH. The reaction was stirred ca. 20 hr. The solvent was removed *in vacuo* and the remaining solid was chilled and made basic by the addition of dilute NaOH. The white solid that formed was extracted with CHCl₃, dried (MgSO₄), and concentrated *in vacuo* to yield a white precipitate. Recrystallization from CHCl₃-hexane gave pure compound. The above conversion could also be accomplished by using anhydrous K₂CO₃ in the place of NaOAc with a 50:50 isopropyl alcohol-ether mixture as solvent.

References

- (1) C. K. Cain, *Annu. Rep. Med. Chem.*, 40 (1969).
- (2) G. I. Poos, J. R. Carson, J. D. Rosenau, A. P. Roszkowski, N. M. Kelley, and J. McGowin, *J. Med. Chem.*, 6, 266 (1963).
- (3) T. K. Todson, C. B. Pollard, and E. C. Reitz, *J. Amer. Chem. Soc.*, 72, 4000 (1950).
- (4) C. D. Nenitzescu and N. Scarlatescu, *Chem. Ber.*, 68, 587 (1935).
- (5) A. F. Growther and L. H. Smith, *J. Med. Chem.*, 11, 1009 (1968).
- (6) M. Leffler and R. Adams, *J. Amer. Chem. Soc.*, 59, 2253 (1937).
- (7) E. W. Bousquet, U. S. Patent 2,434,099 (Jan 6, 1948).
- (8) G. Fodor and K. Koczka, *J. Chem. Soc.*, 850 (1952).
- (9) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, 96, 99 (1949).
- (10) T. Kurihara, O. Keisyke, and I. Naoko, *Tohoku Yakka Daigaku Kenkyu Nempo*, 11, 93 (1964).

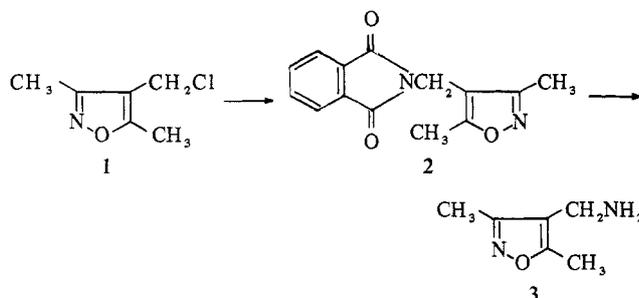
3,5-Dialkyl-4-(phthalimidomethyl)isoxazoles, Pyrazoles, and Isothiazoles. Novel Antiandrogens

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N-[(3,5-Dimethyl-4-isoxazolyl)methyl]phthalimide (2) was found empirically to be an effective, orally active antagonist of exogenous and endogenous androgens. Extensive modification of this molecule was undertaken to determine whether a more active compound could be prepared. Significant activity in this class of compounds was found to be restricted to 3,5-dialkyl- (especially 3,5-dimethyl-) 4-(phthalimidomethyl)isoxazoles, pyrazoles, and isothiazoles, optionally substituted in the aromatic ring by nitro, methoxy, amino, or acetamido groups. The most active compounds in rats, both orally and subcutaneously, were *N*-[(3,5-dimethylpyrazol-4-yl)methyl]phthalimide (42) and its 3-amino analog 52.

4-Chloromethyl-3,5-dimethylisoxazole¹ (1) is an important intermediate in a new steroid total synthesis recently reported by one of us.² In view of the significance of isoxazoles in medicinal chemistry, it appeared attractive to us to prepare

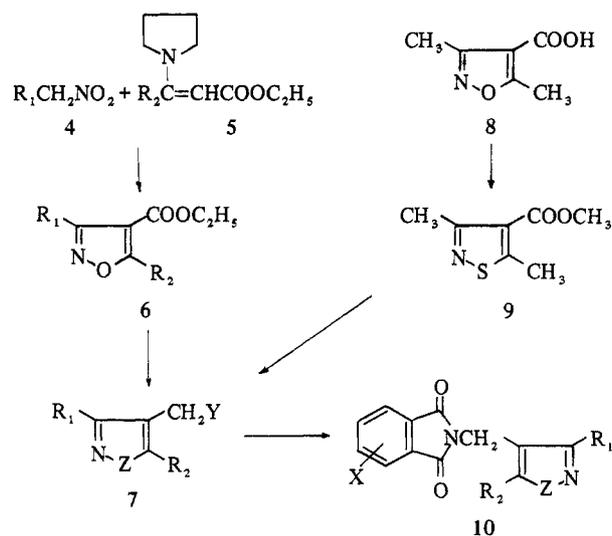


a number of derivatives of 1 containing a second nitrogen atom for biological evaluation. Among the compounds we wished to make was the amine 3. Treatment of the chloride 1 with potassium phthalimide in DMF³ gave, in 78% yield, the phthalimide 2 which, upon hydrazinolysis,⁴ gave the desired amine. Although this compound, as its hydrochloride, did not show any useful biological activity, phthalimide 2 was found to be an effective antagonist of exogenous and endogenous androgens. The preparation and testing of this compound and various analogs constitute the subject of this report.

Chemistry. Several possibilities for chemically modifying *N*-[(3,5-dimethyl-4-isoxazolyl)methyl]phthalimide (2) are evident. Among the changes we have made are (a) modification of the substituents at positions 3 and 5 of the isoxazole ring, (b) substitution of the aromatic portion of the phthalimide ring, (c) conversion of the isoxazole ring to pyrazole or isothiazole, (d) changing the number of CH₂ groups between the two rings, and (e) modification of the nature of the imide ring. The compounds we have prepared are listed in Table I.

Two general synthetic routes were employed. In the first of these (Scheme I), a 4-halomethyl-3,5-dialkylisoxazole or isothiazole 7 was treated in dimethylformamide with potassium phthalimide³ or a substituted phthalimide and K₂CO₃

Scheme I



X = H, 3- or 4-NO₂, 3- or 4-Cl, 3,4,5,6-Cl₄; Y = OH, Cl; Z = O, S; for definitions of R₁ and R₂, see Table I

at elevated temperatures.⁵ With the exception of 4-bromo-methylisoxazole⁶ and 4-chloromethyl-5-methylisoxazole,¹ the chloromethylisoxazoles were prepared by Stork's method.^{7,8} Thus, condensation of the substituted nitromethanes 4 and β-pyrrolidinoacrylates 5 in POCl₃-triethylamine gave the carboethoxyisoxazoles 6, which were reduced with LiAlH₄.† In an early experiment carried out in ether, a violent explosion occurred during hydrolysis. We have found that if the reduction and aqueous destruction of excess hydride are carried out at -30° under N₂, the danger of explosion is minimized (over 100 such reductions on various

† 4-Carboethoxy-3-methyl-5-(*p*-nitrophenyl)isoxazole was not stable under these reaction conditions. It was thus saponified to give the acid⁹ which was reduced by the method of Ishizumi, *et al.*¹⁰ (reaction with ethyl chloroformate followed by NaBH₄ reduction of the resulting carbonic-carboxylic acid anhydride).