The only effective means for the purification of the crude 5-allyluridine was through partition chromatography on a Celite column. A column was prepared by mixing 66 g. of acid-washed Celite 545[6] with 33 ml. of the lower phase of an ethyl acetate–water mixture. The resulting powdery Celite was packed into a column 2.7 cm. wide to a height of 33 cm. The crude nucleoside (1.10 g.) was dissolved in 3.5 ml. of the lower phase and mixed with 7 g. of Celite and packed on top of the column. The column was developed with the upper phase of the ethyl acetate–water mixture. Fractions of about 20 ml. each were collected. The early fractions were colored brown and contained material absorbing ultraviolet light strongly at 226 mμ. 5-Allyluridine was eluted from fractions 23 to 29, and evaporation of these fractions gave a white crystalline solid (0.51 g., 36%), m.p. 171–174°. After recrystallization from ethyl acetate, white feathery crystals were obtained, m.p. 175–176°. The material gave a positive spray test for a 1,2-glycol.[11] The shapes of the ultraviolet absorption curves over a range of pH values appear identical with those of 1-β-D-ribofuranosylthymine,[3] with spectrophotometrically determined pK_a values of 9.9 and above 12. The following data refer to these spectra: $\lambda_{max\ (m\mu)}^{pH\ 7.01}$ 267 (ε 9230); $\lambda_{min\ (m\mu)}^{pH\ 7.01}$ 235 (ε 2090); $\lambda_{max\ (m\mu)}^{pH\ 12\ (0.01\ N\ NaOH)}$ 266 (ε 6790); $\lambda_{min\ (m\mu)}^{pH\ 12\ (0.01\ N\ NaOH)}$ 246 (ε 4530); $\lambda_{max\ (m\mu)}^{pH\ 14\ (1\ N\ NaOH)}$ 268 (ε 7020).

Anal. Calcd. for $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67; N, 9.86. Found: C, 50.52; H, 5.82; N, 9.67.

(11) J. G. Buchanan, C. A. Dekker, and A. G. Long, *J. Chem. Soc.*, 3162 (1950).

6-Ethyl-1,2,4,2H-thiadiazine-3,5(4H,6H)dione 1,1-Dioxide

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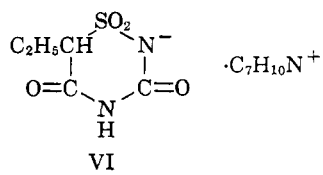
6-Ethyl-1,2,4,2H-thiadiazine-3,5-(4H,6H)dione 1,1-dioxide was synthesized as its 2,6-lutidine salt (VI) for testing as a hypnotic by reactions similar to those used for 1,2,4,2H-thiadiazine-3,5(4H,6H)dione 1,1-dioxide.[2] The reaction sequence employed is shown below.

$$Na^+C_6H_5O_3SCH_2COOC_6H_5^- \longrightarrow C_6H_5O_3SCH(C_2H_5)COOC_6H_5$$
I II

$$\xrightarrow[-33°]{NH_3} C_6H_5O_3SCH(C_2H_5)CONH_2 \xrightarrow[75°]{NH_3}$$
III

$$NH_2SO_2CH(C_2H_5)CONH_2 \xrightarrow{KNCO}$$
IV

$$NH_2CONHSO_2CH(C_2H_5)CONH_2 \longrightarrow$$
V



$\cdot C_7H_{10}N^+$

VI

Alkylation of the sodium derivative of diphenyl sulfoacetate (I) by means of diethyl sulfate in toluene required a period of 7–8 days. In agreement with observations made on the alkylation of malonic ester[3] it was found that the addition of dimethylformamide decreased the reaction time to less than 2 days without sacrificing the yield. Ring closure was accomplished by refluxing V in 2,6-lutidine and gave a crystalline lutidinium salt (VI). The same reaction with pyridine gave an oil which could not be crystallized but which had an infrared spectrum similar to that of the lutidinium salt. Efforts to convert the lutidinium salt to the free thiadiazine were unsuccessful. The use of aqueous systems gave the hydrolysis product, α-carbamylpropanesulfonamide (IV). Acidification in nonaqueous media gave a colorless glass which could not be crystallized. The infrared spectrum of the glass gave little information about the structure because of poor resolution. All of the bands were broad and the peaks were unresolved.

A similar synthesis of 6,6-diethyl-1,2,4,2H-thiadiazine-3,5-(4H,6H)-dione 1,1 dioxide from diphenyl α,α-diethylsulfoacetate failed in the ammonolysis step. The product, after acidification, was polymeric in nature and differed in properties from the 4,4-diethyl-3-keto-1,2-thiazetidine 1,1-dioxide reported to be formed from the diacid chloride.[4] Further work on this product is in progress.

6-Ethyl-1,2,4,2H-thiadiazine-3,5(4H,6H)dione 1,1-dioxide as the lutidine salt (VI) showed no hypnotic activity in mice. Doses of 300–750 mg./kg. intraperitoneally and 1500 mg./kg. orally produced only a slight decrease in the activity in mice.

Experimental[5]

Diphenyl α-Sulfopropionate (II).—To a suspension of sodium powder (15.42 g.) in toluene (1 l.), diphenyl sulfoacetate[2] (196 g.) was added in 20-g. increments. Each portion was added after the evolution of hydrogen had ceased from the preceding portion. The resulting mixture was treated with diethyl sulfate (206 g.) and dimethylformamide (5 ml.) and stirred at 50–75° until the solution became neutral to moist pH paper (1–2 days). Removal of half of the toluene under reduced pressure was followed by filtration of the sodium ethyl sulfate. The latter was washed with 50 ml. of toluene and the combined filtrates were heated under reduced pressure to remove the remainder of the toluene. The excess diethyl sulfate was removed by distillation (0.5 mm.) and the diphenyl α-sulfopropionate was purified by distillation; yield 155 g., b.p. 170–180° (0.15 mm.), $n^{28}D$ 1.5338.

Anal. Calcd. for $C_{16}H_{16}O_5S$: C, 60.00; H, 5.00. Found: C, 60.23; H, 5.15. The infrared spectrum of a film gave principal bands at 5.69 μ (CO), 6.3 μ (C_6H_5), and 7.21, 7.35 μ (SO_3).

Diphenyl α,α-Diethylsulfoacetate.—This ester was prepared in 81% yield from diphenyl α-sulfopropionate in a manner similar to that given for diphenyl α-sulfopropionate. The product boiled at 169–177° (0.15 mm.); $n^{28}D$ 1.5328.

Anal. Calcd. for $C_{18}H_{20}O_5S$: C, 62.05; H, 5.75. Found: C, 61.50; H, 5.62. The infrared spectrum of a film was similar to that of diphenyl α-sulfopropionate and differed only in that the peak for the SO_3 group was sharper and appeared at 7.4 μ.

Phenyl α-Carbamylpropanesulfonate (III).—Diphenyl α-sulfopropionate (2 g.) was dissolved in liquid ammonia (10 ml.) and the ammonia allowed to evaporate. The residue was extracted with cold hexane to remove phenol and then recrystallized from absolute ethanol; yield 0.95 g., m.p. 159–160°.

Anal. Calcd. for $C_{10}H_{13}NO_4S$: C, 49.40; H, 5.35; N, 5.76. Found: C, 49.45; H, 5.16; N, 5.55.

(1) Abstracted in part from the Ph.D. thesis of R. L. Abbott, submitted to the State University of Iowa, February, 1962.

(2) B. E. Hoogenboom, R. L. Abbott, L. Locatell, Jr., and R. L. Hinman, *J. Org. Chem.*, **24**, 1983 (1959).

(3) H. E. Zaugg, B. W. Horrom, and S. Borgwardt, *J. Am. Chem. Soc.*, **82**, 2895 (1960).

(4) B. J. R. Nicolaus, E. Bellasio, and E. Testa, *Helv. Chim. Acta*, **45**, 717 (1962).

(5) Melting points are corrected; boiling points are not corrected.

TABLE I

	Intraperitoneal						Oral			
Dose (mg./kg.)	100	200	300	500	750	1000	200	500	1000	1500
Deaths—Acute	0	0	0	0	0	2	0	0	0	0
—Delayed	0	0	0	0	0	0	0	0	0	0
—Total	0/3	0/3	0/3	0/3	0/3	2/3	0/3	0/3	0/3	0/3
—Time						15–30 min.				
Atoxia	−	−	+	+	+	+ +	−	−	+	+
Decrease in observed spontaneous activity	−	−	+	+ +	+ +	+ +	−	+	+ +	+ +

α-Carbamylpropanesulfonamide (IV).—Diphenyl α-sulfopropionate (49 g.) was heated with liquid ammonia (100 ml.) in a sealed tube at 75° for 12 hr. Removal of the ammonia followed by extraction with ether left a residue which after 2 crystallizations from ethanol gave the diamide; yield 20.5 g., m.p. 174–175°.

Anal. Calcd. for $C_4H_{10}N_2O_3S$: C, 28.91; H, 6.03; N, 16.88. Found: C, 29.09; H, 6.01; N, 17.15.

The infrared spectrum in potassium bromide gave principal bands at 3 μ (NH) broad, 5.96 μ (CO), and 7.55 μ, 8.8 μ (SO_2).

α-Carbamylpropanesulfonylurea (V).—α-Carbamylpropanesulfonamide (IV) (8.95 g.) was added to a finely divided suspension of potassium cyanate (4.5 g.) in refluxing absolute ethanol (150 ml.) and the mixture was refluxed with stirring for 2 hr. The resulting mixture was cooled and the potassium salt of the ureide (11.55 g.) was collected by filtration. The salt was dissolved in water (15 ml.) and acidified with concd. hydrochloric acid (pH 2). The resulting white solid (7.2 g.), which formed after cooling, melted after recrystallization from absolute ethanol at 151–155° dec.

Anal. Calcd. for $C_5H_{11}N_3O_4S$: C, 28.71; H, 5.26, N, 20.10. Found: C, 28.47; H, 5.18; N, 19.75.

The infrared spectrum had bands at 5.80 μ ($NHCONH_2$), 5.95 μ (NH_2COCH), 6.62 μ (?), 7.60 μ, 8.67 μ (SO_2) and was practically identical with that of carbamylmethanesulfonylurea.[2]

Lutidinium 6-Ethyl-1,2,4,2H-thiadiazine-3,5(4H,6H)dione 1,1-Dioxide.—A mixture of α-carbamylpropanesulfonylurea (2.0 g.) and dry 2,6-lutidine (5 ml.) was refluxed for 30 min. At the end of this period a viscous liquid formed which solidified to a glass upon cooling. Decantation of the lutidine was followed by trituration of the glass with acetone. The crystals formed were recrystallized from absoluted ethanol; yield 0.81 g., m.p. 204–206°.

Anal. Calcd. for $C_{12}H_{17}N_3O_4S$: C, 48.20; H, 5.72; N, 14.05. Found: C, 48.32; H, 5.88; N, 14.42.

The infrared spectrum in potassium bromide contained principal bands at 5.9 μ (CO), 6.19 μ (CO), 7.24 μ, 8.8 μ, (SO_2) and resembled that for the sodium salt of 1,2,4(2H)-thiadiazine-3,5-(4H,6H)-dione 1,1 dioxide.[2]

The decanted lutidine upon treatment with ether gave an amorphous solid which when recrystallized from absolute ethanol gave 0.65 g. of α-carbamylpropanesulfonamide.

Reaction of Diphenyl α,α-Diethylsulfoacetate with Liquid Ammonia.—Diphenyl α,α-diethylsulfoacetate (19.5 g.) was sealed with liquid ammonia (40 ml.) in a glass tube and allowed to stand at room temperature for 1 day. Removal of the ammonia was followed by extraction with ether. The remaining solid was refluxed for 30 min. with 75 ml. of absolute ethanol and gave 8.8 g. of a compound melting at 223–224.5° dec.

Anal. Calcd. for $C_{16}H_{14}N_2O_3S$: C, 37.11; H, 7.22. Found: C, 36.77; H, 6.79.

Treatment of this salt with hydrochloric acid followed by solution in dimethylformamide and reprecipitation with ether gave a white solid melting at 218–220° dec. 4,4-Diethyl-1,2-thiazetidine-3-one 1,1-dioxide[4] is reported to melt at 63°.

Anal. Calcd. for $C_6H_{11}NO_3S$: C, 40.70; H, 6.27. Found: C, 40.71; H, 6.63.

Pharmacological Test (Table I).—Groups of 3 mice were dosed with the drug and then watched for gross symptomatology. The degree of the affect was graded from 0 to +++ by an experienced observer. No sleep was observed at any dose level. By comparison pentobarbital produces sleep at 35 mg./kg. intraperitoneally.

Acknowledgment.—The authors wish to thank the Abbott Laboratories for the pharmacological test reported.

Derivatives of 1-Phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine

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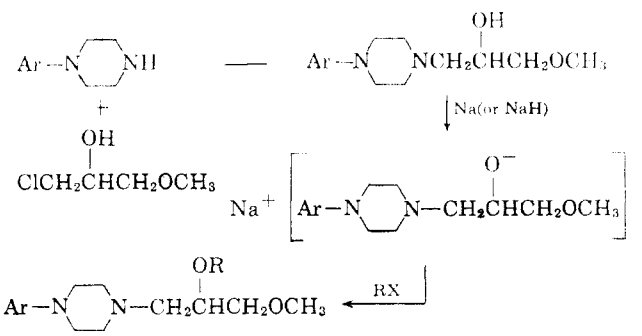
The structural relationship of the piperazines to certain other materials known to have pharmacological activity has prompted the synthesis of several series of piperazine derivatives with potential use as anthelmintic, antihistiminic, and tranquilizing agents. Amino ethers, particularly those of the ethanolamine series, are effective as antihistiminics. A wide variety of piperazine compounds have already been found to have effect upon the central nervous system. These include various dialkyl- and arylalkylpiperazines,[2–6] frequently with a 2-alkoxyethyl, 3-alkoxypropyl, 2-hydroxyethyl, or 3-hydroxypropyl group as one of the N-substituents.

The present work consists of the preparation and characterization of derivatives of 1-phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine. It also includes the synthesis of four new 1-aryl-4-(2-hydroxy-3-methoxypropyl)piperazines and their use in the preparation of the respective methyl ethers. The physical and analytical data for these compounds are given in Table I. The following general procedure was used in these syntheses.



where R = —COO—alkyl or —COC_6H_5.

(1) Deceased. Formerly Professor of Chemistry, University of Florida.
(2) G.m.b.H. Nordmark-Werke, British Patent 813,473 (1959).
(3) Robert F. Parcell, U. S. Patent 2,836,594 (1958).
(4) Walter Voegtli, U. S. Patent 2,800,474 (1957).
(5) H. G. Morren, R. Denayer, R. Linz, J. Mathieu, H. Strubbe, and S. Trolin, *Ind. Chim. Belge*, **22**, 409 (1957).
(6) Armiger H. Sommers, U. S. Patent 2,891,063 (1959).