filtration, washed with aqueous ethanol (5%) and sublimed at 140° (0.7 mm.) to give 0.28 g. (34%) of 2,5-bis-(methylamino)-N-methyl-N'-methyl-3,6-pyrazinedicarboxamide, m.p. 253–254°. No other pure compound could be isolated from the hydrolysis mixture.

Anal. Calcd. for $C_{10}H_{16}N_6O_2$: C, 47.6; H, 6.4; N, 33.3. Found: C, 47.7; H, 6.4; N, 33.1.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF DELAWARE]

Spiro-1'-benzenesulfonylpiperidine-4',5-barbituric Acid and Related Derivatives of Isonipecotic Acid

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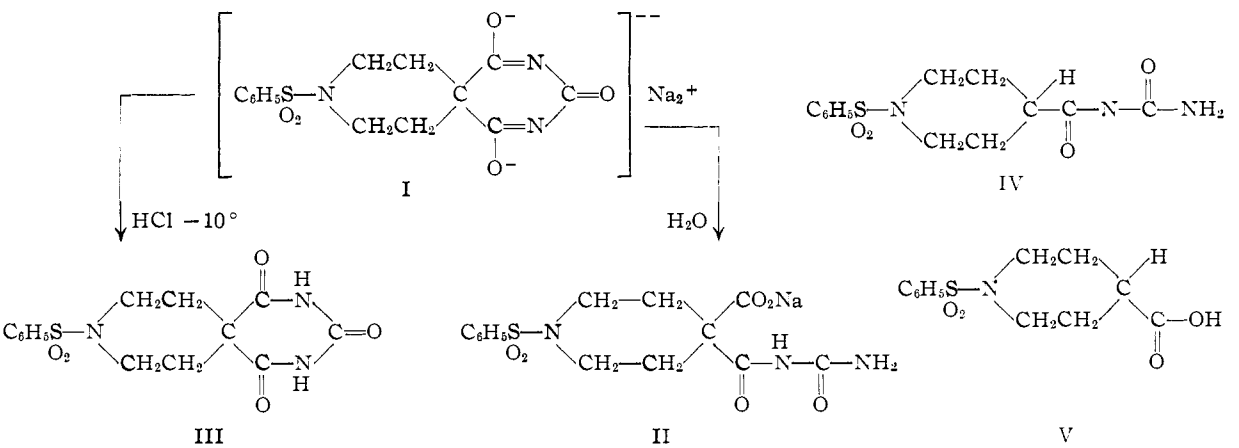
A derivative of spiropiperidine-4',5-barbituric acid has been synthesized. The piperidine ring has the same effect as the cyclopentane ring in increasing both the ease of formation of the barbituric acid and the cleavage of the barbituric acid ring by aqueous alkali. Some isonipecotic acid derivatives have been prepared and subjected to pharmacological examination.

The instability of spirocyclopentane-1,5'-barbituric acid toward cold aqueous alkali has been described in a previous report.[1] This behavior, aside from the possible pharmacological interest, seemed to afford justification for the synthesis and study of a spiropiperidine derivative III which contains the same number of carbon atoms in the derived ring.

N-Benzenesulfonyldiethanolamine dibenzenesulfonate was prepared from benzenesulfonyl chloride and diethanolamine in a yield of 80%. This by condensation with sodiomalonic ester in benzene gave the needed 4,4-dicarboxyethyl-1-benzenesulfonylpiperidine (83%), which reacted with urea to give sodium spiro-1'-benzenesulfonylpiperidine-4',5-barbiturate (I) in nearly quantitative yield. The last reaction



took place with great ease at 40°. This is in agreement with previously reported cases[1] of the effect of rings in facilitating the reaction. By quickly mixing the salt with a freezing mixture of hydrochloric acid and ice the desired spiro acid III was obtained.

The spiro acid by standing in aqueous alkaline solution was hydrolyzed first to the salt II, the acid of which could be isolated after standing one hour. Further standing for eleven days converted II to the ureide of 1-benzenesulfonylisonipecotic acid (IV). This was hydrolyzed to 1-benzenesulfonylisonipecotic acid (V) when refluxed with sodium hydroxide in a solution of alcohol and water. The identical acid also was made from 1-benzenesulfonylpiperidine-4,4-dicarboxylic acid through the loss of carbon dioxide by heat.

The acid chloride of V when heated gradually with urea gave the identical ureide IV. The acid chloride also reacted smoothly to yield the amide and the esters, but a mixture of products was obtained by its action with hydrazine. The methyl ester was found to be much superior as a reagent for the synthesis of 1-benzenesulfonylisonipecotylhydrazine (Table I).

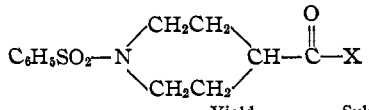
The above amide gave 56% inhibition[2] at 0.2 mg./cc. in the *in vitro* tuberculosis test, no hypnosis at 400–900 mg./kg. in rats, and 20% protection by the electro shock and no protection by the metrazol method at 400 mg./kg. *per os*. The hydrazide at 0.2 mg./cc. gave 68% inhibition in the tuberculosis test. In mice it was ineffective against influenza virus, MM virus, streptococcus pyogenes, typhoid, klebsiella pneumoniae and pseudomonas aeruginosa. The ureide at 0.2 mg./cc. gave no inhibition in the tuberculosis test, no hypnosis at 400–900 mg./kg. by mouth in rats and 20% protection by the electroshock but no protection by the metrazol method at 400 mg./kg. *per os*. The spirobarbituric acid III by vein in rats produced convulsions in-

(1) G. S. Skinner, George Limperos and R. H. Pettebone, THIS JOURNAL, **72**, 1648 (1950).

(2) Pharmacological tests by Eli Lilly and Company.

TABLE I

DERIVATIVES OF ISONIPECOTIC ACID



X	M.p., °C.	Yield, %	Sulfur, % Calcd.	Found
-OH	160	87	11.90	11.62
$-NH_2$	206–206.5	92	20.13[a]	20.07[a]
$-OCH_3$	85	95	11.31	11.28
$-OC_2H_5$	85.5	91	10.78	10.79
$-NHNH_2$	134.5	92	11.31	11.28
$-NHCONH_2$	205.5–206	90	10.30	10.29

[a] $-CONH_2$ instead of S.

stead of hypnosis. It had LD_{50} = 210 mg./kg.

Experimental

N-Benzenesulfonyldiethanolamine Dibenzenesulfonate.—A mixture of 630 g. (8 moles) of dry reagent grade pyridine and 70 g. (0.67 mole) of diethanolamine was cooled in a bath of ice and salt while protected from moisture. While the temperature was kept at 0–5°, 388.5 g. (2.20 moles) of benzenesulfonyl chloride was added dropwise with stirring in the course of two hours. In another half-hour the reaction product began to cake so badly that the stirrer was stopped and elevated above the surface. After standing overnight the contents of the flask were shaken with a freezzing mixture of 500 g. of finely crushed ice and 500 cc. of hydrochloric acid (1.19). Additional outside cooling was employed as needed until the disintegrated solid was ready to filter with suction. It then was washed six times with ice-cold water. The yield of dry crude product was 282 g. (80%). It was crystallized twice from chloroform to yield fine, white monoclinic crystals, m.p. 128–129°.

Anal. Calcd. for $C_{22}H_{23}O_6NS_3$: S, 18.29. Found: S, 18.19.

Diethyl 1-Benzenesulfonylpiperidine-4,4-dicarboxylate.—To a stirred mixture of dry benzene (900 cc.) and sodiomalonic ester prepared from 128 g. (0.80 mole) of malonic ester and 9.2 g. (0.40 mole) of sodium sand were added 105 g. (0.20 mole) of the above tribenzenesulfonyl derivative. The mixture was then refluxed on a steam-bath for 20 hours. The cooled mixture required 2 cc. of hydrochloric acid (1.19) for neutralization. The supernatant liquid was decanted after the heavy solid had settled. The residue was treated with 200 cc. of cold water and extracted twice with 25-cc. portions of benzene. The benzene and diethyl malonate were removed under diminished pressure, finally at 1 mm. with careful control of the bath temperature. The residue was dissolved in 100 cc. of hot alcohol and the solid which separated at salt–ice-bath temperature was filtered with suction and washed with 50% alcohol, yield 125 g. (85%), m.p. 68–69°. Recrystallization from alcohol gave 120 g. of white crystals, m.p. 70°.

Anal. Calcd. for $C_{17}H_{13}O_6NS$: S, 8.60. Found: S, 8.57.

Spiro-1′-benzenesulfonylpiperidine-4′,5-barbituric Acid.—To a solution of sodium ethoxide prepared from 3.44 g. of sodium and 60 cc. of absolute alcohol were added 18.4 g. (0.049 mole) of diethyl 1-benzenesulfonylpiperidine-4,4-dicarboxylate and 6.0 g. (0.10 mole) of urea with stirring at 40°. After a half-hour a solid began to cake along the wall of the flask. Stirring was discontinued in an hour and the reaction mixture was kept at this temperature for four hours longer. The next day the salt was filtered with the aid of a rubber dam and washed several times with alcohol. The yield of the salt dried *in vacuo* over calcium chloride was 18.6 g. (99%).

Anal.[3] Calcd. for $C_{14}H_{13}O_5N_3SNa_2$: Na, 12.07. Found: Na, 11.95.

The sodium salt was added to a rapidly stirred mixture of ice and hydrochloric acid. The precipitated barbituric acid derivative was filtered with suction, washed with cold very dilute hydrochloric acid and dried *in vacuo* over potassium hydroxide; yield 15.7 g. (93%). After crystallization from glacial acetic acid the spirobarbituric acid derivative melted at 278–280° dec. The neutralization equivalent was determined by titration in aqueous acetone solution using phenolphthalein as the indicator.

Anal. Calcd. for $C_{14}H_{15}O_5N_3S$: S, 9.47; neut. equiv., 337. Found: S, 9.47; neut. equiv., 337.

Hydrolysis of the Spirobarbituric Acid Derivative to the Ureide IV.—The above compound (3.37 g., 0.010 mole) was dissolved in a solution of 0.50 g. (0.0125 mole) of sodium hydroxide in 25 cc. of water at room temperature. In two hours the acid from an aliquot portion melted at 125–130° dec., solidified and then remelted at 195–200°. The acid was acid to congo red and soluble in sodium bicarbonate solution. After nine days the acid product sintered at 127–130° and then melted at 203–206°. The remainder of the mixture was acidified on the eleventh day. This product, after one crystallization from alcohol, did not sinter at the lower temperatures and did not evolve gas or change in appearance in a bath at 170–180°. One more crystallization from alcohol gave the pure ureide IV of the derivative of isonipecotic acid as clusters of needles (Table I). It was insoluble in cold dilute sodium hydroxide solution.

The spirobarbituric acid derivative did not dissolve or change in appearance when boiled with 6 *N* hydrochloric acid. The melting point of the recovered product was unchanged.

1-Benzenesulfonyl-4-carboxyisonipecotylurea.—A solution of 1.0 g. (0.0030 mole) of III in 7.5 cc. of 10% sodium hydroxide was allowed to stand for one hour. Carbon dioxide was passed into the solution for 15 minutes and the very small amount of precipitate was filtered. Acidification of the filtrate to *p*H 3–4 gave an oil which crystallized after standing overnight; dec. p. 128°, yield 0.85 g. (81%). It had dec. p. 128° also after crystallization in the form of colorless plates from ether. When heated at 140° it gave IV as shown by constancy of the melting point of the mixture with the sample prepared from the acid chloride.

Anal. Calcd. for $C_{14}H_{17}N_3O_6S$: S, 9.02; Found: S, 9.02.

1-Benzenesulfonylpiperidine-4,4-dicarboxylic Acid.—Four grams of the diethyl ester was refluxed for three hours in a roomy flask with 60 cc. of a solution (25%) of sodium hydroxide. The acid was precipitated while the mixture was kept cold in ice and was crystallized once from water and once from alcohol; the crystals decomposed at 124°.

Anal. Calcd. for $C_{11}H_{13}O_2NS(CO_2H)_2$: neut. equiv., 156.6. Found: neut. equiv., 156.5.

The acid was converted by thionyl chloride to the acid chloride which gave the diamide. This was purified by crystallization from alcohol; m.p. 223–224° dec.

Anal. Calcd. for $C_{13}H_{17}O_4N_3S$: S, 10.29. Found: S, 10.27.

1-Benzenesulfonylisonipecotic Acid.—The ureide IV (0.3 g.) was refluxed with a mixture of 15 cc. of sodium hydroxide (20%) and 2 cc. of alcohol for two hours. The finely divided acid separated slowly after acidification at 0°. It was washed with ice-cold water; m.p. 159–160°.

1-Benzenesulfonylpiperidine-4,4-dicarboxylic acid was heated at 170° until the evolution of carbon dioxide was complete. The product obtained by crystallization from alcohol melted at 160° and was identical with the above sample. The over-all yield from 35 g. of the above diethyl ester was 23 g. (Table I).

1-Benzenesulfonylisonipecotamide.—The solid reaction product obtained by the action of 1.3 g. (0.011 mole) of thionyl chloride on 1 g. (0.0037 mole) of the acid V under reflux for a half-hour at 60–65° followed by distillation of excess thionyl chloride was added gradually to 1.4 g. (0.016 mole) of aqua ammonia (0.90). The dry white crystalline crude product melted at 195–198.5°. It was crystallized twice from 35 cc. of alcohol washing sparingly each time with 50% alcohol; yield 0.92 g. The carboxamide group was determined by hydrolysis to ammonia (Table I).

Esters of 1-Benzenesulfonylisonipecotic Acid (V).—The acid chloride from 1.0 g. (0.0037 mole) of V was cooled, treated with 1.0 g. (0.031 mole) of methyl alcohol and warmed with stirring to 70°. The solid was then dissolved by the addition of 2 cc. of methyl alcohol, the solution was filtered and the methyl ester was then precipitated by the gradual addition of ice-cold water. The white granular precipitate was filtered and washed with water several times. The crude product (m.p. 84–85°) was purified by

(3) Analysis by Bernard Freedman.

one crystallization from a minimum amount of methyl alcohol. The ethyl ester was prepared in a similar manner, and similar yields (Table I) were obtained when larger quantities were prepared.

1-Benzenesulfonylisonipecotylhydrazine.—To a refluxing mixture of 8 g. (0.24 mole) of hydrazine (95%) and 10 cc. of methyl alcohol was added rapidly dropwise a solution of 15.18 g. (0.054 mole) of methyl 1-benzenesulfonylisonipecotate in 125 cc. of methyl alcohol. The solution was refluxed for two hours and then distilled to one-half its volume. The crystalline product which separated on standing was filtered with suction and washed sparingly three times with methyl alcohol, yield 14.0 g. (Table I). It was purified for analysis by crystallization from 100 cc. of alcohol. The yield obtained from the ethyl ester was only 50% of the theoretical.

1-Benzenesulfonylisonipecotylurea from the Acid Chloride.—A mechanically stirred mixture of 8.5 g. (0.14 mole) of powdered urea and the acid chloride from 3 g. (0.011 mole) of 1-benzenesulfonylisonipecotic acid was heated gradually to 130° where it was maintained for one hour. After cooling the cake was disintegrated by 50 cc. of hot alcohol and the solid was filtered from the cold mixture; yield 3.0 g., m.p. 204–205°. It was purified by dissolution in a hot mixture of 65 cc. of alcohol and 17 cc. of water. The hot filtrate was cooled finally in a salt–ice-bath whereupon it crystallized in the form of colorless fine needles.

NEWARK, DELAWARE

CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF LAKESIDE LABORATORIES, INC.]

Antispasmodics. II. Derivatives of N-Substituted-3-piperidols

BY JOHN H. BIEL, EDWIN P. SPRENGELER, HELEN A. LEISER, JACK HORNER, ALEXANDER DRUKKER AND HARRIS L. FRIEDMAN

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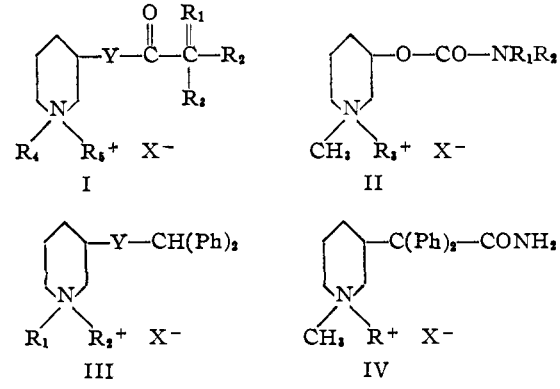
The initial finding that the replacement of diethylaminoethyl by N-ethyl-3-piperidyl in some standard antispasmodic agents yielded compounds of superior spasmolytic activity prompted a more general investigation of the therapeutic usefulness of a variety of 3-piperidyl derivatives. Five classes of compounds were synthesized: (1) substituted acetic acid esters of 3-hydroxypiperidine and 3-mercaptopiperidine derivatives; (2) substituted carbamates of N-methyl-3-hydroxypiperidine; (3) N-substituted-3-piperidyl benzhydryl ethers, as well as their thioisosteres; (4) *p*-aminobenzoates of N-alkyl-3-piperidol; (5) N-methyl-3-piperidyldiphenylmethyl derivatives R—C(Ph)$_2$Y; Y = CONH$_2$, CN. The first series of compounds yielded a number of potent antispasmodic agents, of which the disubstituted hydroxyacetates appeared to be the most promising ones. The carbamates in series (2) either inhibited or potentiated acetylcholine spasms in the guinea pig ileum depending on the type of substituent. The benzhydryl ethers (series 3) were active spasmolytic agents. Quaternization of the nitrogen produced a tenfold increase in spasmolytic activity. The compounds in series (4) were local anesthetics comparable to procaine in potency. The diphenylacetamide derivatives (5) were moderate antispasmodics. Phenyl-2-thienylglycolic acid was obtained *via* a mixed benzoin condensation followed by a benzilic acid type rearrangement. The preparation of 3-mercaptopiperidines is described. A general method for obtaining N-aryl-substituted carbamates was developed.

A new amino alcohol has always been a challenge to the medicinal organic chemist for the synthesis of therapeutically useful derivatives. The ready availability of N-alkyl-3-hydroxypiperidines by the method of Paul and Tchelitcheff[1] prompted a long-range investigation in these laboratories of N-substituted-3-piperidyl derivatives as substitutes for the aminoalkyl portion in a large variety of physiologically active compounds.

The first paper in this series[2] dealt exclusively with substituted acetic acid esters of N-alkyl-3-hydroxypiperidines. Several of these derivatives have since been shown to be pharmacologically potent antispasmodic agents[3–6] and clinically efficacious drugs in the treatment of gastrointestinal spasms.[7–10] The present paper is a report on the chemistry and preliminary pharmacology on five types of 3-piperidyl derivatives: (1) substituted acetic acid esters (I, R_1 = H, OH, CH_2OH; R_2 = H, phenyl, 2-thienyl, cyclohexyl, cyclopentyl; R_3 = H, phenyl, *n*-propyl; R_4 = methyl, ethyl, isopropyl, *n*-butyl, 2-phenylisopropyl; R_5 = H, methyl, *n*-butyl; X = Cl, Br, I, citrate; Y = O, S);



(2) disubstituted carbamates (II, R_1 = methyl, *n*-butyl, phenyl; R_2 = methyl, *n*-butyl, phenyl, benzyl; R_3 = H, CH_3; X = Cl, Br, I); (3) benzhydryl ethers (III, R_1 = methyl, ethyl; R_2 = H or methyl; X = Cl, Br; Y = O, S); (4) *p*-aminobenzoates of N-alkyl-3-hydroxypiperidine; (5) N-alkyl-3-piperidyldiphenylmethyl derivatives (IV, R = H, CH_3; X = Br, mono- or dihydrogen citrate). The substituted acetic acid esters were prepared by

(1) R. Paul and S. Tchelitcheff, *Compt. rend.*, **221**, 560 (1945).

(2) J. H. Biel, H. L. Friedman, H. A. Leiser and E. P. Sprengeler, THIS JOURNAL, **74**, 1485 (1952).

(3) J. Y. P. Chen and H. Beckman, *J. Pharmacol. Exptl. Therap.*, **104**, 269 (1952).

(4) J. Y. P. Chen, *Federation Proc.*, **13**, 343 (1954).

(5) P. L. Ewing and L. D. Seager, *J. Pharmacol. Exptl. Therap.*, **106**, 385 (1952).

(6) J. P. Long and H. H. Keasling, *Federation Proc.*, **13**, 380 (1954).

(7) H. Necheles, H. Laski, L. D. Elegant and R. Baum, *Am. J. Digestive Diseases*, **21**, 121 (1954).

(8) B. Weinberg, R. Ginsberg and H. Sorter, *ibid.*, **20**, 230 (1953).

(9) F. Steigmann and R. A. Dolehide, *Federation Proc.*, **13**, 408 (1954).

(10) N-Ethyl-3-piperidyl diphenylacetate hydrochloride (JB305), Dactil Lakeside Laboratories, is marketed as a general antispasmodic.