TABLE I

SALTS OF α-AMINO-*p*-TOLUENESULFONAMIDE

No.	Salt	Acid added to base in EtOH: Acid	Solvent	Molar ratio base:acid	Yield, %	Mp, °C	Formula	Calcd, %: Acid[a]	Base[b]	Other	Found, %: Acid	Base	Other
1	Acetate	Acetic	None	1:1	91	169.0–172.0	$C_7H_{10}N_2O_2S \cdot C_2H_4O_2$	24.4		N, 11.38	24.1		N, 11.10
2	Carbamate	CO_2	None	1:0.7[d]	95	153.4–154.5	$(C_7H_{10}N_2O_2S)_2 \cdot CO_2$		89.4	CO_2, 10.6		89.5	CO_2, 10.0
3	Citrate	Citric·H_2O	2-Propanol	1:0.33	75	158.6–161.0	$(C_7H_{10}N_2O_2S)_3 \cdot C_6H_8O_7$	25.6	74.4		25.1	71.9	H_2O, 0.4[c]
4	Fumarate	Fumaric	DMF	1:0.5	99	208.0–209.5	$(C_7H_{10}N_2O_2S)_2 \cdot C_4H_4O_4$	23.8	76.2		23.4	75.7	
5	Succinate	Succinic	DMF	1:0.5	100	211.5–212.2	$(C_7H_{10}N_2O_2S)_2 \cdot C_4H_6O_4$	24.1	75.9		24.1	75.7	

[a] Lithium methoxide titration. [b] Acetous perchlorate titration. [c] Karl Fischer titration. [d] Excess CO_2 used; theoretical ratio 1:0.5.

while the acetate caused little or no change in the same parameters.

The same authors reported that the acute intravenous toxicity of the acetate was significantly less than that of the hydrochloride salt, in both mouse and rat. The 24 hr intravenous LD_{50} values are 900 ± 52 and 1580 ± 101 mg/kg, respectively, in the mouse; and 1170 ± 74 and 2040 ± 139 mg/kg, respectively, in the rat, for HCl and HOAc salts of α-amino-*p*-toluenesulfonamide.

Experimental Section

To a stirred solution of 1 mole of α-amino-*p*-toluenesulfonamide in 2 l. of boiling ethanol, the equivalent amount of the acid, dissolved in a suitable solvent, was added over a period of 15–20 min. The resulting thick slurry was cooled to 10° and the solid was filtered. The filter cake, after having been pressed hard under a rubber dam, was washed with alcohol and dried at 60° *in vacuo*. No recrystallization was carried out. The yields ranged from 75 to 100%.

The carbamate salt was prepared directly by saturation of a warm (50°) solution of the base with excess CO_2. The data are summarized in Table I.

Bisoxime Sulfonates and Bisquaternary Hydrazones

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The important class of antineoplastic compounds known as alkylating agents includes the nitrogen mustards, bis- and trisethylenimine derivatives, bisepoxides, and bismethanesulfonate esters. Common to all of these alkylating agents is their possession of at least two functional groups which can interact readily with biological nucleophiles, in some cases by way of carbonium ions and in others by way of nucleophilic displacement, affording cross-linking and inactivation of the nucleic acids and possibly other cell constituents.[1] The distance between the alkylating centers is important, and this variable was particularly suitable for study in the case of the bismethanesulfonate esters.[2]

Consideration of the structure and reactivity of bisoxime sulfonates [$RSO_2ON{=}CR'(CH_2)_nCR'{=}NOSO_2R$] led us to hope that this type of compound might also have the cross-linking properties of the established alkylating agents. Oxime sulfonates are highly reactive, undergoing facile solvolysis (Beckmann rearrangement) and incorporating a variety of nucleophiles such as amines, alcohols, and phosphate anions.[3] A second type of compound which offered similar theoretical possibilities was the bisquaternary hydrazones [$(CH_3)_3N^+N{=}CR(CH_2)_nCR{=}NN^+(CH_3)_3$].[4] Another interesting feature for this type is that, although we are not aware of any literature examples, a direct nucleophilic displacement on nitrogen is at least a theoretical possibility. This possibility affords a distinction to the classical alkylating agents wherein nucleophilic attack must take place on carbon. Of further interest in this type was the possibility of preparing compounds in which appropriate separation of the two positively charged nitrogen atoms would afford pertinent analogs of the well-known hypotensive bisquaternary amines.[5]

We therefore undertook the preparation of a series of simple bisoxime sulfonates and bisquaternary hydrazones,[6] with emphasis on variation of the distance between the two reactive groups. The bissulfonates of diketoximes were prepared conveniently by treatment with methane- or *p*-toluenesulfonyl chloride in pyridine. Bismethanesulfonates were prepared from 1,2-cyclohexanone dioxime and 1,4-cyclohexanone dioxime, and bis-*p*-toluenesulfonates were prepared from dimethylglyoxime and 2,5-hexanedione dioxime (Table I). The last-mentioned compound was prepared by addition of the sulfonyl halide to a suspension, in benzene, of the disodium salt of the dioxime. Not surprisingly, no bissulfonates of dialdoximes could be obtained by these techniques.[8] Condensation with excess 1,1-dimethyl-

(1) D. F. Gamble, H. W. Bond, and A. Burger in "Medicinal Chemistry," A. Burger, Ed., 2nd ed, Interscience Publishers, Inc., New York, N. Y., 1960, p 1083.

(2) G. R. Greenberg, *Federation Proc.*, **12**, 651 (1953).

(3) W. Z. Heldt, *J. Am. Chem. Soc.*, **80**, 5880 (1958), and references cited therein.

(4) P. A. S. Smith and E. E. Most, Jr., *J. Org. Chem.*, **22**, 358 (1957).

(5) A. Burger in "Medicinal Chemistry," A. Burger, Ed., 2nd ed, Interscience Publishers, Inc., New York, N. Y., 1960, p 509.

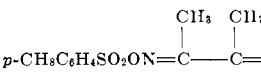
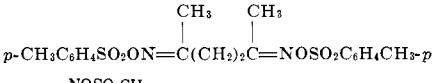
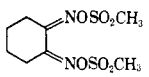
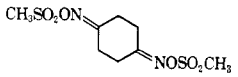
(6) Prior to this investigation reports on only two bisoxime *p*-toluenesulfonates[7] and no bisquaternary hydrazones could be found in the literature.

(7) I. L. Knunyants and B. P. Fabrichnyi, *Dokl. Akad. Nauk SSSR*, **68**, 701 (1949); G. I. Glover and H. Rapoport, *J. Am. Chem. Soc.*, **86**, 3397 (1964).

(8) The elimination of substituents from aldoxime derivatives constitutes a general method of nitrile synthesis (R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, p 598). In several attempted preparations of aldoxime *p*-toluenesulfonates, we detected, by infrared absorption spectra, the formation of nitrile groups.

TABLE I

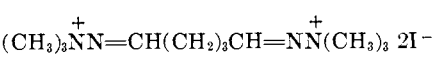
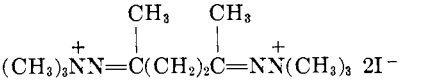
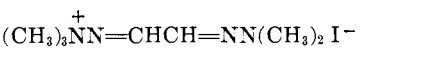
BISOXIME SUFFONATES

Compound	Mp, °C[a]	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % S	Found, % C	Found, % H	Found, % N	Found, % S
	183–185	60	$C_{18}H_{20}N_2O_6S_2$	50.93	4.75	6.60	15.11	51.22	4.63	6.72	14.93
	126–127	20	$C_{20}H_{24}N_2O_6S_2$	53.08	5.35	6.19	14.17	53.32	5.81	6.21	13.67
	160	30	$C_8H_{14}N_2O_6S_2$	32.20	4.73	9.39	21.50	32.58	4.80	9.65	21.31
	134–135	56	$C_8H_{14}N_2O_6S_2$	32.20	4.73	9.39	21.50	32.57	4.85	9.51	20.80

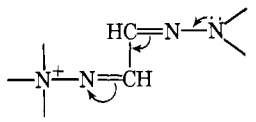
[a] Melting points (corrected) were determined on a Mel-Temp melting point apparatus.

TABLE II

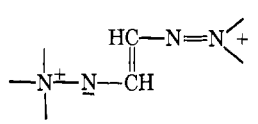
BIS- AND MONO-1,1,1-TRIMETHYLHYDRAZONIUM IODIDES

Compound	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % I	Calcd, % N	Found, % C	Found, % H	Found, % I	Found, % N
	183	$C_{11}H_{26}I_2N_4$	28.22	5.56	54.25	11.97	28.25	5.89	53.95	11.66
	221–224	$C_{12}H_{28}I_2N_4$	29.89	5.85	52.64	11.62	29.40	6.01	52.88	11.43
	195	$C_7H_{17}IN_4$	29.59	5.98	44.66	19.71	29.56	6.06	44.13	19.37

hydrazine afforded bisdialkylhydrazones[9] of both diketones and dialdehydes. The ease of conversion of these bisdialkylhydrazones into their methiodide salts varied with structure. Thus, the bis-1,1-dimethylhydrazone of 1,5-pentanedione reacted vigorously and instantaneously with methyl iodide forming the corresponding bistrimethylhydrazonium diiodide, whereas this same type of reaction was much slower with the bis-1,1-dimethylhydrazone of 2,5-hexanedione. The quaternary hydrazones are listed in Table II. Inspection of molecular models reveals more steric crowding in the trimethylhydrazonium salts of ketones than in the corresponding salts of aldehydes, and this property might explain the observed rate differential. That the bis-1,1-dimethylhydrazone of glyoxal forms only a monotrimethylhydrazonium iodide salt would appear to contradict this explanation; however, in this instance the two hydrazone groups are in conjugation and the formation of a positive charge on one group should deactivate the other as illustrated in A and B.[10]



A



B

Pharmacology.—The bisoxime tosylates and bisquaternary hydrazones described in this note were all found inactive when tested against the 72_J mammary adenocarcinoma in mice at dose levels of 250 mg/kg.[11] The bisquaternary hydrazones did not exhibit useful hypotensive properties,[12] despite the fact that in the two examples prepared (Table II) the distances between positively charged nitrogen atoms (seven and six atoms) afford reasonable approximations to the optimum distances required for hypotensive activity in the bisquaternary amines.[5]

Experimental Section

Bisoxime sulfonates were prepared by treating a solution of the dioxime in the minimum of dry pyridine at ice-bath temperature with 2 equiv of methanesulfonyl chloride or *p*-toluenesulfonyl chloride, usually on a 20-mmole scale. The resulting mixture was kept at room temperature for 16 hr, then treated with ice–water; the precipitate of crude sulfonate was dried in a vacuum oven and crystallized from CH_2Cl_2–hexane. However, the bistosylate of 2,5-hexandione dioxime was prepared by first treating with 2 equiv of $NaOCH_3$ in benzene for 48 hr. The mixture was then cooled in an ice bath and treated with 2 equiv of *p*-toluenesulfonyl chloride. After 16 hr the precipitate that formed was dried and crystallized from CH_2Cl_2–hexane. The results of these preparations of bisoxime sulfonates are given in Table I.

Bis-1,1,1-trimethylhydrazonium Diiodides and 1,1-Dimethylhydrazone-1′,1′,1′-trimethylhydrazonium Iodides.—A mixture of the dialdehyde or diketone, 2 equiv of 1,1-dimethylhydrazine, and sodium-dried benzene was heated in a Dean–Stark apparatus until the theoretical amount of water was collected. These preparations were usually done on an 0.1-molar scale in 200 ml of benzene. The benzene solution was then concentrated, and the residue was distilled under vacuum. From terephthalic dialdehyde, the residue was a solid and was crystallized from acetone–water (no distillation). A commercially available, 20% aqueous solution of 1,5-pentanedione was used directly (water removed by the Dean–Stark apparatus). In general, the bis-1,1-dimethylhydrazones were unstable liquids which rapidly darkened on exposure to air and did not give good combustion analyses. They were converted directly into the corresponding hydrazonium salts as described below. One exception to this

(9) The bisthiosemicarbazone of 2-oxo-3-ethoxybutyraldehyde, a compound having slight analogy to these bisdialkylhydrazones, was reported to have activity against Walker carcinosarcoma, Sarcoma 180, and others by E. Mihich and C. A. Nichol, *Cancer Res.*, **25**, 1410 (1965).

(10) The bis-1,1-dimethylhydrazone of terephthalic dialdehyde (see Experimental Section) also has the two hydrazone groups in conjugation, and it too, gave only a monomethiodide salt. Completely satisfactory analyses were not obtained for this salt.

(11) For a complete description of the antitumor assay procedure, see A. W. Vogel and J. D. Haynes, *Cancer Chemotherapy Rept.*, **22**, 23 (1962); E. H. Dearborn, *Acta Unio Intern. Contra Cancrum*, **15** (Suppl), 76 (1959).

(12) No measurable effect on the blood pressure of conscious normotensive rats at 100 mg/rat *po* was observed.

rule was the bis-1,1-dimethylhydrazone of terephthalic dialdehyde, mp 162–163°, which gave the following analytical data.

Anal. Calcd for $C_{10}H_{18}N_4$ (218.30): C, 66.02; H, 8.31; N, 25.67. Found: C, 66.40; H, 8.33; N, 25.27.

The hydrazonium iodides of the above mentioned bis-1,1-dimethylhydrazones were prepared by treating these hydrazones with a large excess of methyl iodide. With the bishydrazone of 1,5-pentanedione, an immediate, vigorous, exothermic reaction ensued and the product was obtained in 86% yield. In all other instances significant heat evolution was not observed, and the solid products separated after several hours or more. The mono-1,1,1-trimethylhydrazonium iodide of glyoxal bis-1,1-dimethylhydrazone formed rapidly, but the bis derivative could not be prepared even on heating at steam-bath temperature in a pressure bottle for 5 hr. A solid product was obtained on treatment of 1,4-cyclohexanedione bis-1,1-dimethylhydrazone with methyl iodide. However, this product was extremely unstable and could not be purified. The quaternary hydrazonium iodides are given in Table II.

Acknowledgments.—We wish to thank Drs. A. Vogel and A. Sloboda for the tumor testing, Dr. J. Cummings for hypotensive assays, and Mr. L. M. Brancone and staff for the microanalytical data.

The Synthesis and Tranquilizer Activity of 2- and 4-Substituted 3,5-Morpholinediones[1a]

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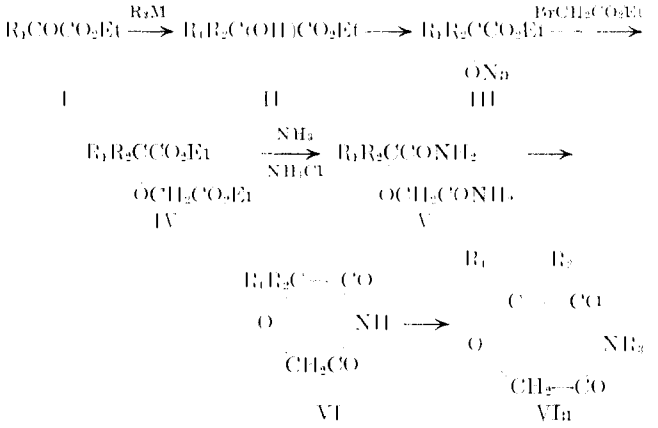
3,5-Morpholinediones (VI and VIa) possess many of the chemical groupings considered to be efficacious in central nervous system depressants.[2] 3,5-Morpholinediones, moreover, are isosteric to barbiturates and glutarimides[3] and thus may be anticipated to approximate these two chemical classes in their CNS depressant properties. Some 3,5-morpholinediones have in the past been tested for hypnotic activity and for other CNS depressant manifestations.[3,4]

Heretofore, only a handful of 3,5-morpholinediones had been prepared. The classical preparative method,[5] utilizing thermally induced cyclizations of diglycolamides (V) (Scheme I) is limited to derivatives free of bulky substituents. New cyclization procedures, herein reported, had to be developed in order to prepare 3,5-morpholinediones bearing bulky substituents in the 2 position.

SCHEME I



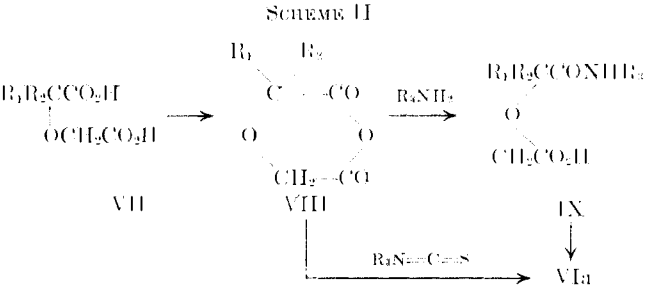
Animal testing of both known and novel 3,5-morpholinediones (see Table IV) has shown at least one compound, VI-10, comparable to glutethimide[6] as a pentylenetetrazole antagonist. A good correlation has been demonstrated between pentylenetetrazole antagonist activity in rats and mild tranquilizer activity.[7]

Synthesis.—3,5-Morpholinediones (VI), the cyclic imides of diglycolic acids (VII), were prepared by converting suitably substituted esters (II) of glycolic acid (Table I) to diesters (IV) of diglycolic acid, then to diglycolic diamides (V) (Table II) which were then cyclized to the title products (VI, Scheme I). Cyclization of the diamides (V) was effected by either sublimation from P_2O_5, or treatment with sodamide, followed by hydrolysis with alcoholic HCl. Simple melting of the diamide was occasionally successful.

N-Methyl groups (R_3) were introduced using diazomethane, converting VI to VIa (Table III). The required substituted glycolic esters II (Table I) were prepared by (a) esterification of commercially available glycolic acids or (b) by treatment of accessible α-keto esters (I) with organometallic reagents.

As an alternative method of preparing N-substituted 3,5-morpholinediones VIa, the anhydrides VIII of diglycolic acids VII were treated with an isothiocyanate[8] or a suitable amine, then cyclized to VIa (Scheme II).

SCHEME II



Pharmacology. Method.—Pentylenetetrazole antagonist activity was measured in rats by the following procedure. The drugs were first administered orally to groups of rats by gastric intubation. One hour later the rats were injected intravenously with 24 mg/kg of pentylenetetrazole (concentration 9.9 mg/ml). The injection was made rapidly into the lateral

(1) (a) Abstract of part of the Ph.D. thesis submitted to the University of Kansas, Dec 1960, by F. A. B. (b) To whom inquiries should be addressed: Box 1042, Clifton, N. J.

(2) W. J. Close and M. A. Spielman in "Medicinal Chemistry," Vol. V, W. A. Hartung, Ed., John Wiley and Sons, Inc., New York, N. Y., 1961, p 44 ff.

(3) G. S. Skinner and J. B. Bicking, *J. Am. Chem. Soc.*, **76**, 2776 (1954).

(4) K. W. Wheeler in "Medicinal Chemistry," Vol. VI, E. E. Campaigne and W. H. Hartung, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p 198.

(5) (a) E. Jungfleisch and M. Godchot, *Compt. Rend.*, **145**, 72 (1907); (b) P. Vieles, *Ann. Chim.*, **3**, 143 (1935); (c) M. Godchot and P. Vieles, *Bull. Soc. Chim. France*, **5**, 1614 (1938); (d) P. Vieles and G. Gasquet, *ibid.*, **10**, 231 (1943); (e) G. Skinner, J. Bickings, and J. Lovett, *J. Org. Chem.*, **24**, 1587 (1959).

(6) E. Tagmann, E. Sury, and K. Hoffman, *Helv. Chim. Acta*, **35**, 1511 (1952).

(7) D. Tedeschi, unpublished observations.

(8) C. Hurd and A. Prapas, *J. Org. Chem.*, **24**, 388 (1959).