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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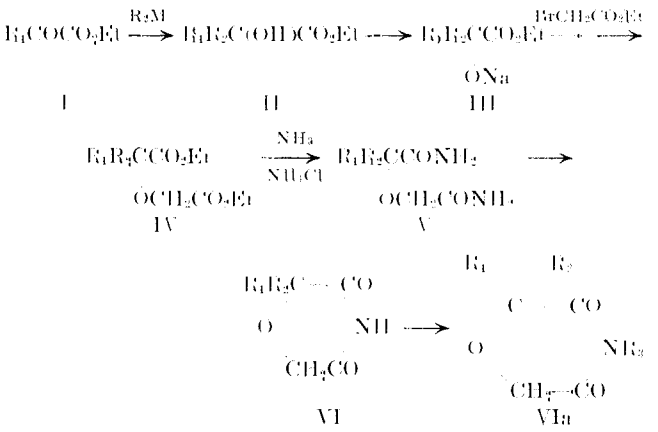
3,5-Morpholinediones (VI and VIa) possess many of the chemical groupings considered to be efficacious in central nervous system depressants.[2] 3,5-Morpholinediones, moreover, are isosteric to barbiturates and glutarimides[3] and thus may be anticipated to approximate these two chemical classes in their 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



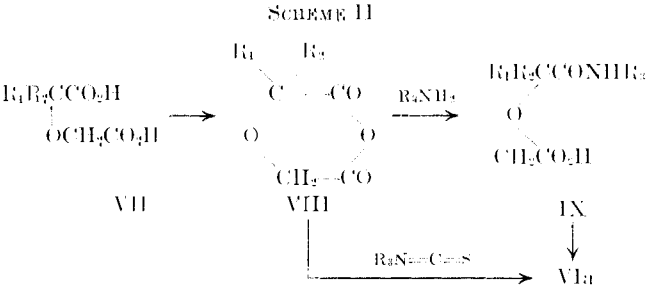
Animal testing of both known and novel 3,5-morpholinediones (see Table IV) has shown at least one compound, VI-10, comparable to glutethimide[6] as a pentylenetetrazole antagonist. A good correlation has been demonstrated between pentylenetetrazole antagonist activity in rats and mild tranquilizer activity.[7]

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. Ghsquet, *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. Frapas, *J. Org. Chem.*, **24**, 388 (1959).

TABLE I
ESTERS OF GLYCOLIC ACIDS (II)
$R_1R_2C(OH)CO_2C_2H_5$

No.	R_1	R_2	Bp, °C (mm)	$n^{25}D$	Method[a]	Yield, %	Formula	% carbon Calcd	% carbon Found	% hydrogen Calcd	% hydrogen Found
I-1	C_6H_5	$H_2CCH{=}CH_2$	117 (2.6)	1.5135	B	31	$C_{13}H_{16}O_3$	70.9	71.0	7.3	7.3
I-2	C_6H_5	$H_2CC{\equiv}CH$	132 (3.7)	1.5180	B	82	$C_{13}H_{14}O_3$	71.6	71.7	6.5	6.7
I-3	C_6H_5	$H_2CC_6H_5$	170–172 (1.4)	1.5535	A	33	$C_{17}H_{18}O_3$	75.5	75.4	6.7	6.8
I-4	C_2H_5	$H_2CCH{=}CH_2$[b]	58–110 (0.7)	1.4584	A	17	$C_9H_{16}O_3$	62.8	62.9	9.3	9.2
I-5	C_6H_5	$H_2CCH_2CH(CH_3)_2$	112–125 (1.5)	1.4880	A	26	$C_{15}H_{22}O_3$	72.0	72.5	8.9	9.1

[a] A, reaction of an α-keto ester with Grignard reagent containing R_2; B, reaction of an α-keto ester with zinc and alkyl halide of R_2 (Reformatsky reaction). [b] For precursor see E. Vogel and H. Schinz, *Helv. Chim. Acta*, **33**, 116 (1950).

caudal vein after which each rat was observed during 5 sec or more for the occurrence of uninterrupted clonic seizure activity. Rats which fail to exhibit such seizure activity are considered protected. Drugs which afford significant protection under these circumstances are investigated further to establish their respective times of peak effect. The dose effective in preventing pentylenetetrazole-induced convulsions in 50% of rats (ED_{50}) and 95% fiducial limits are calculated by the Litchfield and Wilcoxon[9] graphic log probit method.

Results (See Table IV).—Only one of the compounds in the series demonstrated any significant activity (VI-10). Although its ED_{50} was less than that of glutethimide, the difference in potency between the two compounds is not statistically significant. Moreover, the ratio of the dose producing signs of neurological deficit to the ED_{50} in the pentylenetetrazole antagonist test was approximately 1.5 for VI-10. This indicates that VI-10 is not a particularly selective pentylenetetrazole antagonist and in this respect resembles glutethimide which also possesses a ratio slightly greater than 1.

Experimental Section[10]

General Methods for the Preparation of II. Method A. Ethyl α-Phenyl-α-(3-methylbutyl)glycolate (II-5).—A Grignard reagent prepared from 0.28 mole of 1-bromo-3-methylbutane was added dropwise to an ether solution of 0.27 mole of ethyl phenylglyoxalate at 0°. After completion of addition, the mixture was refluxed 2 hr and stripped, and the residue was hydrolyzed with cold, dilute HCl. After extraction with ether, drying, and distillation a 26% yield of II-5 was obtained.

Method B. Ethyl α-Allyl-α-phenylglycolate (II-1).—A mixture of 24 g (0.2 mole) of freshly distilled allyl bromide and 36 g (0.2 mole) of ethyl phenylglyoxalate[5a] in dry ether was added to 24 g of zinc[11] in a 1:1 mixture of tetrahydrofuran–ether (both dry). After several hours of stirring, the black mixture was hydrolyzed with ice and dilute HCl, extracted with ether, dried, and distilled, affording 13.3 g (31%) of II-1.

General Preparation of IV. Ethyl α-Phenyl-α-(3-methylbutyl)-α-carbomethoxymethoxyacetate (IV-4). Williamson Reaction.—To a suspension of 3.15 g (0.08 mole) of sodamide in dry toluene was added, in a dropwise manner, a dry toluene solution of 20.2 g (0.08 mole) of ethyl α-phenyl-α-(3-methylbutyl)-glycolate (II-5) and the mixture was stirred and refluxed for 3 hr. A toluene solution of 20 g (0.13 mole) of methyl bromoacetate was added dropwise to the opaque mixture, and the mixture was stirred, refluxed for 3 hr, cooled, and washed with water. Distillation afforded a 16% yield of IV-4.

General Method of Preparation of V. α-Phenyl-α-propargyldiglycolamide (V-2).—A mixture of 5.50 g (0.02 mole) of ethyl α-phenyl-α-propargyl-α-carbomethoxymethoxyacetate (IV-2) and 0.2 g of NH_4Cl was cooled in a Pyrex tube in Dry Ice–solvent as excess liquid NH_3 was introduced. While still immersed in Dry Ice, the tube was sealed and placed in an iron container, rocked several times in order to mix the two liquid phases, and allowed to stand undisturbed at 60° for 7 days. The sealed tube was again immersed in Dry Ice, then carefully broken open, and its volatile contents were allowed to evaporate. A white solid residue remained, which, when recrystallized from methanol, afforded a 73% yield of V-2.

General Preparation of VI. 2-Phenyl-2-propargyl-3,5-morpholinedione (VI-8). Method A.—A suspension of 0.46 g (0.0002 mole) of α-phenyl-α-propargyldiglycolamide (V-2) and excess sodamide in dry benzene was stirred and refluxed for 2 hr. Refluxing for more than 2 hr resulted in the formation of a red-orange side product. The suspension was stripped of benzene under mild vacuum, and the gray powder residue then was refluxed for 1 hr in 30 ml of 50% ethanol, acidified with 8 ml of concentrated HCl.[12] The orange ether extract was stripped and the semisolid residue (VI-8) (60% yield) was recrystallized from benzene–ligroin.

Method B.—An intimate solid mixture of 0.15 g (0.0006 mole) of V-2, excess P_2O_5, and trace amounts of Cu powder was sublimed at 170° under vacuum for several hours.[13] The sublimate was dissolved in ether–benzene, washed with water, and allowed to evaporate slowly. The yield was less than 20%.

Method C. N-Methyl-2,2-dimethyl-3,5-morpholinedione (VI-a-7).—After several unsuccessful attempts at preparing this compound from 2,2-dimethyl-3,5-morpholinedione[5e] (VI-7) employing reagents such as dimethyl sulfate and methyl iodide, diazomethane was found to methylate VI-7. A dry ether solution of CH_2N_2 (from 2.4 g of N-nitrosomethylurea) was added to 1.64 g (0.01 mole) of VI-7 in dry ether, and the solution was allowed to stand for 2 days at 10°. After filtration, the filtrate was distilled to afford a 20% yield of VI-a-7.

Method D. N-Benzyl-3,5-morpholinedione (VI-a-9).—To 6.30 g (0.05 mole) of diglycolic anhydride[14] an equimolar quantity of benzylamine (5.5 g) was added rapidly,[15] and the mixture was stirred vigorously. The cooled crystalline product of addition, the amide acid (IX-1), was then heated at 160–175° (2.5 mm) for[16] 3.5 hr, and finally distilled at 147°. The colorless distillate solidified as 3.2 g (27%) of a solid waxy material.

Method E. N-Phenyl-2,2-dimethyl-3,5-morpholinedione (VI-a-5).—A mixture of 3.24 g (0.22 mole) of α,α-dimethyldiglycolic acid anhydride[5e] (VIII-2) and 3.20 g (0.22 mole) of phenyl isothiocyanate was refluxed in dry pyridine for 20 hr.[8] After removal of the pyridine, the viscous residue was distilled between 35 and 72° (3.2 mm), the distillate solidifying in the receiver. Recrystallization from ethanol afforded pure white crystals of VI-a-5 in 12% yield.

α,α-Biphenylenediglycolamide (V-5).—9-Hydroxy-9-fluorenecarboxylic acid was prepared from phenanthraquinone following the method of Bistrzycki[17] in 60% yield and then converted to the methyl ester as reported by Staudinger,[18] in 86% yield. Treatment of the ester's sodio derivative with methyl or ethyl bromoacetate afforded the diglycolates IV-5 and IV-6, respectively, in 37 and 43% yields. Quantitative yields (4.7 g) of the dianiide were obtained either by dissolving 5.20 g (0.017 mole)

(9) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).

(10) All melting points were obtained on a Thomas–Hoover type open capillary melting point apparatus and are corrected. Boiling points are uncorrected. Elemental microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

(11) P. Karrer, C. Eugster, and M. Recordati, *Ber.*, **89**, 360 (1956).

(12) J. Rakshit, *J. Chem. Soc.*, **103**, 1557 (1913).

(13) P. Brown, D. Spiers, and M. Whalley, *J. Chem. Soc.*, 2882 (1957).

(14) R. Anschutz and F. Biernaux, *Ann.*, **273**, 65 (1893).

(15) L. Rice, E. Reid, and C. Grogan, *J. Org. Chem.*, **19**, 891 (1954).

(16) N. Searle, U. S. Patent 2,444,536 (July 6, 1948).

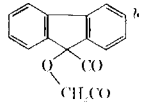
(17) A. Bistrzycki and Z. Zaleska, *Ber.*, **45**, 1439 (1912).

(18) H. Staudinger, *ibid.*, **39**, 3895 (1906).

TABLE II

NOVEL DERIVATIVES OF DIGLYCOLIC ACIDS (IV AND V)

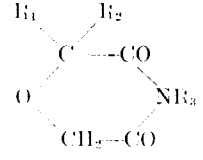
$YOCCH_2OCR_1R_2COX$

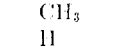
No.	R_1	R_2	X	Y	Bp (mm) or mp, °C	$n^{25}D$	Method[a]	% yield	Formula	% carbon Calcd	% carbon Found	% hydrogen Calcd	% hydrogen Found	% nitrogen Calcd	% nitrogen Found
IV-1	$H_2CCH{=}CH_2$	C_6H_5	OEt	OMe	131–151 (0.4)	1.5069	C	11	$C_{16}H_{20}O_5$	65.7	65.6	6.9	7.0		
V-1	$H_2CCH{=}CH_2$	C_6H_5	NH	NH	137.0–138.3		E	97	$C_{13}H_{16}N_2O_3$	62.9	62.7	6.5	6.6	11.3	11.4
IV-2	$H_2CC{\equiv}CH$	C_6H_5	OEt	OMe	170–172 (1.7)	1.5103	C	39	$C_{16}H_{18}O_5$	66.2	67.0	6.3	6.5		
V-2	$H_2CC{\equiv}CH$	C_6H_5	NH_2	NH_2	201.0–202.6		E	73	$C_{13}H_{14}N_2O_3$	63.4	63.7	5.7	5.8	11.4	11.7
V-3	$H_2CC_6H_5$	C_6H_5	NH_2	NH_2	219.1–220.6		E	55	$C_{17}H_{18}N_2O_3$	68.5	68.7	6.1	6.3	9.4	9.4
IV-4	$CH_2CH_2CHMe_2$	C_6H_5	OEt	OMe	160–174 (1.5)	1.4930	C	16	$C_{18}H_{26}O_5$	67.0	67.0	8.1	8.1		
IV-5			OMe	OMe	98.2–99.1		C	37	$C_{18}H_{16}O_5$	69.3	69.3	5.2	5.2		
IV-6			OMe	OEt	96.5–97.8		D	43	$C_{19}H_{18}O_5$	70.0	70.4	5.6	5.9		
V-5			NH_2	NH_2	252.9–253.4		E	99	$C_{18}H_{19}N_2O_3$	68.1	68.3	5.0	5.0	9.9	9.8
IV-7	C_6H_5[c]	C_6H_5	OEt	OEt	170–193 (2.0)	1.5340	D	42	$C_{20}H_{22}O_5$	70.1	70.9	6.5	6.6		
V-7	C_6H_5	C_6H_5	NH_2	NH_2	195.8–197.1		D	35	$C_{16}H_{16}N_2O_3$	67.6	67.8	5.7	5.6	9.9	10.0
IX-1	C_6H_5	C_6H_5	OH	NH_2	185.7–186.9		...	10	$C_{16}H_{15}NO_4$	67.4	67.3	5.3	5.2	4.9	4.9

[a] A, Williamson reaction between II and ethyl chloroacetate; B, Williamson reaction between II and ethyl bromoacetate; C, Williamson reaction between II and methyl bromoacetate; D, treatment of diester IV with alcoholic NH_3; E, treatment of diester IV with liquid NH_3 in sealed tube. [b] For precursors see ref 17 and 18. [c] For precursors see S. Arcez, *Ber.*, **37,** 2766 (1904).

TABLE III

NOVEL 3,5-MORPHOLINEDIONES (VI AND VII)



VI	R_1	R_2	R_3	Bp (mm) or mp, °C	$n^{25}D$	Method[a]	% yield	Formula	% carbon Calcd	% carbon Found	% hydrogen Calcd	% hydrogen Found	% nitrogen Calcd	% nitrogen Found
1	C_6H_5	C_6H_5	H	111.5–112.5	...	B	15	$C_{16}H_{13}NO_3$	71.9	72.0	4.9	4.9	5.2	5.2
						A	6							
2	$CH_2CH{=}CH_2$	C_6H_5	H	97.4–98.2	...	A	83	$C_{13}H_{13}NO_3$	67.5	67.3	5.7	5.8	6.1	6.1
3	C_6H_5	C_6H_5	CH_3	59.8–60.9		C	57	$C_{17}H_{15}NO_3$	72.6	73.0	5.4	5.6	5.0	5.0
a-4	CH_3[b]	CH_3	$C_2H_4C_6H_5$	134–138 (4.5)	1.5204	D	25	$C_{13}H_{17}NO_3$	68.0	68.3	6.9	6.9	5.7	5.8
a-5	CH_3	CH_3	C_6H_5	95.1–96.0		E	12	$C_{12}H_{13}NO_3$	65.7	65.9	6.0	6.0	6.4	6.3
a-6	CH_3	CH_3		60–62 (1.7)	1.4868	D	31	$C_{19}H_{22}N_2O_3$	57.7	57.7	8.2	8.4	10.4	10.3
a-7	H_3C	H_3C	CH_3	52 (1.7)	1.4682	C	28.1	$C_7H_{11}NO_3$	53.5	53.2	7.0	7.0	8.9	8.9
8	C_6H_5	$CH_2C{\equiv}CH$	H	149.1–150.5	...	A	60	$C_{13}H_{11}NO_3$	68.1	68.1	4.9	5.0	6.1	5.9
						B	20							
a-9	H	H	$CH_2C_6H_5$	53.1–54.0	...	D	27	$C_{11}H_{11}NO_3$	64.4	64.4	5.4	5.5	6.8	6.8
10	C_6H_5[c]	CH_3	H	78.9–80.2		A	85	$C_{11}H_{11}NO_3$	64.4	64.6	5.4	5.5	6.8	6.8
11	C_6H_5[d]	H	H	120.1–121.3		F	15	$C_{16}H_{13}NO_3$	62.8	63.1	4.8	4.9	7.3	7.2

[a] A, treatment of V with $NaNH_2$, then aqueous HCl; B, sublimation of V from P_2O_5; C, treatment of VI with CH_2N_2; D, treatment of anhydride VIII with amine, then heat; E, treatment of anhydride VIII with C_6H_5NCS; F, heating amide V at melting point. [b] For precursors see ref 5e. [c] For precursors: H. Wren and E. Wright, *J. Chem. Soc.*, **119,** 798 (1921). [d] For precursors see ref 5a.

TABLE IV
PENTYLENETETRAZOLE ANTAGONIST ACTIVITY OF 3,5-MORPHOLINEDIONES

No.	Pentylenetetrazole antagonist act. Dose, mg/kg *po*	% of rats protected	Rat dosage, mg/kg
VI-1	100	0	200, NOE[a]
VI-2	50	0	...
VI-a-3			300, NOE
VI-a-4	100	0	300, 3/3 exophthalmos 1/3 miosis
VI-a-5	100	20	300, NOE
VI-a-6	100	0	300, NOE
VI-7	82	0	300, NOE
VI-8	25	0	...
VI-a-9	100	17	300, NOE
VI-10	ED_{50} = 33.75 mg/kg		Ataxia ED_{50} = ~50 mg/kg
VI-11	100	0	100, miosis, vocalization when touched

[a] NOE = no overt effects.

of IV-5 in methanol and passing dry NH_3 through the solution, or by sealing 3.60 g (0.01 mole) of IV-5 in a Pyrex tube with excess liquid NH_3 and allowing the tube to remain at 80° for 4 days. Recrystallization from methanol gave 3.1 g (99%) of pure cylindrical crystals. All attempts at cyclizing the diamide to the morpholinedione failed.

Infrared Spectra of 3,5-Morpholinediones.—Infrared spectra of N-unsubstituted 3,5-morpholinediones VI have the following set of bands in common, and which seem to be characteristic of VI; ν (in CCl_3H) 2.9 (N–H str), 3.05–3.25, 5.79 a single wide band with shoulders (C=O str), 6.6, 6.92, 7.2, 7.5, 7.7, 7.9, 8.1 (str and broad), 8.3–8.5, 8.8, 9.05 μ.

The N-substituted (VIa) 3,5-morpholinediones differ from VI in that the 2.9-μ band is missing, and the carbonyl region has two bands at *ca.* 5.72 and 5.93 μ rather than a single band.

Acknowledgment.—The authors thank Smith Kline and French Laboratories for financial support of these studies.

Some Derivatives of 8-Thia-3-azabicyclo[3.2.1]octane

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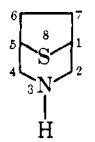
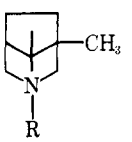
Received July 11, 1966

Compounds containing the 8-thia-3-azabicyclo[3.2.1]octane ring system have been described by Turner and Hill,[2] and Horak,[3] but the unsubstituted parent compound (I) and its N-substituted derivatives have not been previously reported. The preparation



I

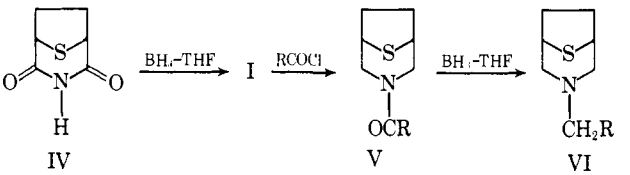


II

III

of these compounds was undertaken because of the reported hypotensive properties of 3-aza-1,8,8-trimethylbicyclo[3.2.1]octane (II)[4] and a variety of other interesting pharmacological properties of 3,8-diazabicyclo[3.2.1]octanes (III).[5]

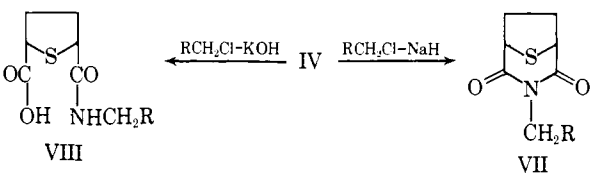
Compound I was obtained in 75% yield by the reduction of IV[3] with diborane in tetrahydrofuran. Acylation under Schotten–Baumann conditions proceeded smoothly to give the N-benzoyl (Va) and the N-phenylacetyl (Vb) derivatives. The N-benzyl (VIa) and N-phenethyl (VIb) derivatives were obtained by the diborane reduction of Va and Vb, respectively (see Table I).



IV V VI

a, R = C_6H_5
b, R = $CH_2C_6H_5$

Compound VIa was also prepared by first treating IV with sodium hydride and benzyl chloride in dimethylformamide to give the N-benzyl-2,4-dioxo derivative (VIIa), followed by diborane reduction. When



VIII VII

a, R = C_6H_5
b, R = C_6H_4Cl-*p*
c, R = $C_6H_3Cl_2$-3, 4

the benzylation was performed in ethanolic potassium hydroxide, as described by Horak,[3] the thiazine ring was cleaved and the tetrahydrothiophene derivative (VIIIa) was isolated. Similar results were obtained with the *p*-chlorobenzyl and 3,4-dichlorobenzyl derivatives.

Oxidation of IV with hydrogen peroxide in glacial acetic acid gave 8-thia-3-azabicyclo[3.2.1]octane-2,4-dione 8,8-dioxide (IX). Reaction of I with *p*-nitrobenzenesulfonyl chloride gave the 3-*p*-nitrophenylsulfonyl compound (X), which was subsequently reduced to the 3-(*p*-aminophenylsulfonyl)-8-thia-3-azabicyclo[3.2.1]octane (XI).

Pharmacology.—The effectiveness of the compounds reported herein as possible hypotensive agents was measured on anesthetized cats. The drugs were dissolved in saline solution and injected intravenously in doses of 2, 5, 10, and 100 mg/kg of body weight.

Of the compounds tested, only Va and Vb were of interest, showing a sustained moderate decrease in blood pressure at 100 mg/kg. Compounds VIa, VIb, VIIIa, and VIIIc caused an unsustained fall in blood pressure, whereas X produced a slight, sustained *hypertensive* effect. The other compounds were inactive.

(1) To whom inquiries concerning this publication should be sent.
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(5) C. Cignarella, E. Occelli, and E. Testa, *J. Med. Chem.*, **8**, 326 (1965), and preceding papers.