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

F. FRIED, RAJ NANDAN PRASAD,[1] AND ALAN P. GAUNCE

Research Department, Abbott, Laboratories Ltd., Montreal, Quebec Canada

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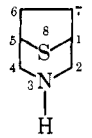
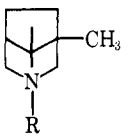
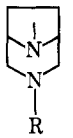
Compounds containing the 8-thia-3-azabicyclo[3.2.1]octane ring system have been described by Turner and Hill,[2] and Horak,[3] but the unsubstituted parent compound (I) and its N-substituted derivatives have not been previously reported. The preparation



I



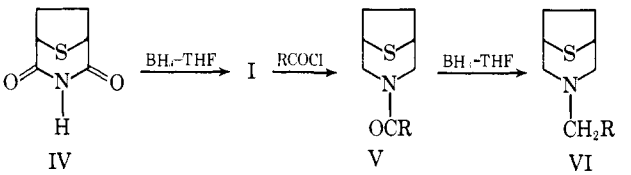
II



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]

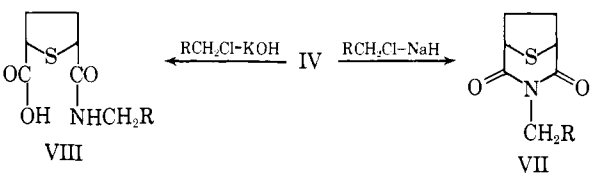
Compound I was obtained in 75% yield by the reduction of IV[3] with diborane in tetrahydrofuran. Acylation under Schotten–Baumann conditions proceeded smoothly to give the N-benzoyl (Va) and the N-phenylacetyl (Vb) derivatives. The N-benzyl (VIa) and N-phenethyl (VIb) derivatives were obtained by the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

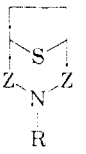
Pharmacology.—The effectiveness of the compounds reported herein as possible hypotensive agents was measured on anesthetized cats. The drugs were dissolved in saline solution and injected intravenously in doses of 2, 5, 10, and 100 mg/kg of body weight.

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.
(2) R. J. Turner and A. J. Hill, *J. Org. Chem.*, **14**, 476 (1949).
(3) V. Horak, *Chem. Listy*, **44**, 34 (1950); *Chem. Abstr.*, **46**, 103 (1952).
(4) C. H. Grogan and L. M. Rice, *J. Org. Chem.*, **22**, 1223 (1957).
(5) C. Cignarella, E. Occelli, and E. Testa, *J. Med. Chem.*, **8**, 326 (1965), and preceding papers.

TABLE I

8-THIA-3-AZABICYCLO[3.2.1]OCTANE AND ITS DERIVATIVES



Compd	Z	R	Yield,[a] %	Mp, °C	Recrystn solvent[b]	Formula	Calcd, % C	H	N	S	X[c]	Found, % C	H	N	S	X[c]
I	CH_2	H	75	273.5–275.5	B–E	$C_6H_{12}NS \cdot HCl$	43.25	7.19	8.70	19.70	21.59 (Cl)	43.49	7.30	8.45	19.35	21.39 (Cl)
Va	CH_2	C_6H_5CO	53	99.5–100.5	M–W	$C_{13}H_{15}NOS$	66.92	6.48	6.01	13.74	6.86 (O)	66.86	6.48	6.02	13.81	6.65 (O)
Vb	CH_2	$C_6H_5CH_2CO$	85	115.5–116.5	Et–P	$C_{14}H_{17}NOS$	67.98	6.93	5.66	12.96	6.47 (O)	68.22	7.11	5.46	13.07	6.52 (O)
VIa	CH_2	$C_6H_5CH_2$	95[d]	211.5–213.5	C–P	$C_{13}H_{17}NS \cdot HCl$	61.01	7.09	5.48	12.53	13.86 (Cl)	61.26	7.12	5.44	12.31	14.03 (Cl)
VIb	CH_2	$C_6H_5CH_2CH_2$	70	235.5–236.5	A–P	$C_{14}H_{19}NS \cdot HCl$	62.31	7.17	5.19	11.88	13.14 (Cl)	62.14	7.37	5.35	12.17	13.20 (Cl)
VIIa	C=O	$C_6H_5CH_2$	63	109–110	E	$C_{13}H_{13}NO_2S$	63.13	5.30	5.66	12.96	12.94 (O)	62.83	5.83	5.79	13.31	13.03 (O)
VIIb	C=O	p-$ClC_6H_4CH_2$	30	90.5–91	E	$C_{13}H_{12}ClNO_2S$[e]	55.41	4.29	4.97	11.38	12.58 (Cl)	55.51	4.38	4.86	11.37	12.34 (Cl)
VIIc	C=O	3,4-$Cl_2C_6H_3CH_2$	32	89.5–91	E	$C_{13}H_{11}Cl_2NO_2S$[f]	49.38	3.51	4.43	10.14	22.42 (Cl)	49.63	3.66	4.35	10.19	22.12 (Cl)
X	CH_2	p-$NO_2C_6H_4SO_2$	83	192–193.5	A–P	$C_{12}H_{14}N_2O_4S_2$	45.84	4.49	8.91	20.40	20.36 (O)	45.87	4.61	8.76	20.65	20.16 (O)
XI	CH_2	p-$NH_2C_6H_4SO_2$	74	197.5–198.5	C–P	$C_{12}H_{16}N_2O_2S_2$	50.68	5.67	9.85	22.55	11.25 (O)	50.42	5.31	10.89	22.17	11.18 (O)

[a] Yields given are those of the crude solid. [b] Recrystallization solvents: A = acetone, B = benzene, C = $CHCl_3$, E = ethanol, Et = ether, M = methanol, P = petroleum ether, W = water. [c] Particular element determined is indicated in parentheses. [d] Yield 85% from VIIa and diborane, and 95% from Va and diborane. [e] *Anal.* Calcd: O, 11.36. Found: O, 11.33. [f] *Anal.* Calcd: O, 10.12. Found: O, 10.29.

Experimental Section[6]

8-Thia-3-azabicyclo[3.2.1]octane (I).—A solution of IV[3] (30.0 g, 0.19 mole) in tetrahydrofuran (200 ml) was added to 2.5% diborane[7] in tetrahydrofuran (460 ml) at −5° with vigorous stirring in a nitrogen atmosphere. After the addition was complete (15 min), the mixture was refluxed for 1.5 hr, cooled to 20°, and hydrolyzed by careful addition of 50% aqueous tetrahydrofuran (110 ml), then 18% HCl (100 ml). The organic solvent was removed by distillation, and the residue was basified with concentrated NaOH solution at 20°. The alkaline mixture was extracted with four 100-ml portions of $CHCl_3$ and the extract was dried and concentrated. The residual oil was taken up in absolute ether, and dry HCl was bubbled through at 5°. The product separated as the **hydrochloride**, mp 270.5–273.5°.

3-Benzoyl-8-thia-3-azabicyclo[3.2.1]octane (Va).—Benzoyl chloride (16.0 g, 0.1 mole) was slowly added to a mixture of I (HCl salt, 16.0 g, 0.1 mole) and NaOH (10.0 g, 0.25 mole) in water (300 ml) at 10°. The crystalline solid which separated was filtered and washed with water: mp 98–100°, ν_{max} 1630 cm^{-1} (C=O).

3-Phenylacetyl-8-thia-3-azabicyclo[3.2.1]octane (Vb) was similarly prepared from I and phenylacetyl chloride: mp 115.5–116.5°, ν_{max} 1640 cm^{-1} (C=O).

3-Benzyl-8-thia-3-azabicyclo[3.2.1]octane (VIa).—Compound Va (5.83 g, 0.025 mole) in tetrahydrofuran (25 ml) was reduced with diborane (by the procedure described for the preparation of I) to yield VIa as the **hydrochloride** (mp 207–211°): ν_{max} 2500 (s), 1500 (m) cm^{-1} (amine salt). Reduction of VIIa (19.8 g, 0.08 mole) in tetrahydrofuran (30 ml) by the same procedure gave VIa.

Vb was similarly reduced to give VIb.

3-[(*p*-Nitrophenyl)sulfonyl]-8-thia-3-azabicyclo[3.2.1]octane (X).—A solution of *p*-nitrobenzenesulfonyl chloride (8.86 g, 0.04 mole) in pyridine (30 ml) was gradually added to a solution of crude I (prepared from 6.64 g (0.04 mole) of the hydrochloride) in pyridine (20 ml) at room temperature. The mixture was stirred at 100° for 10 min, and then poured into water at 5° yielding yellow crystals, mp 186.5–191.5°.

3-*p*-Aminophenylsulfonyl-8-thia-3-azabicyclo[3.2.1]octane (XI).—Powdered stannous chloride (11.4 g, 0.06 mole) was added gradually to a well-stirred solution of X (6.3 g, 0.02 mole) in concentrated HCl (40 ml). After the addition was complete, the temperature of the reaction mixture was gradually raised to 85°, held at 85–95° for 1.5 hr, cooled to 10°, made strongly alkaline with concentrated NaOH solution, and extracted with $CHCl_3$. The extract was washed with water, and dried. Concentration gave XI: mp 195.5–197.5°; ν_{max} 3450 (s), 3370 (s) cm^{-1} (NH_2).

3-Benzyl-8-thia-3-azabicyclo[3.2.1]octane-2,4-dione (VII).—A solution of IV[4] (15.8 g, 0.1 mole) in dimethylformamide (DMF) (70 ml) was slowly added to a well-stirred suspension of sodium hydride (4.6 g, 0.11 mole; 56% suspension in oil) in DMF (80 ml) at room temperature. The temperature rose to 50° in 10 min, and a clear solution was obtained. It was cooled to 10°, and benzyl chloride (14 g, 0.11 mole) in DMF (15 ml) was added slowly. After 2 hr at 85–100°, the mixture was hydrolyzed with water (600 ml) at 5°. The white precipitate was separated and crystallized from ethanol (mp 104.5–108.5°): ν_{max} 1725, 1670 cm^{-1} (C=O). Horak[3] reported that he obtained this substance (mp 114°) from IV and benzyl chloride in the presence of NaOH.

3-(*p*-Chlorobenzyl-8-thia-3-azabicyclo[3.2.1]octane-2,4-dione (VIIb) and 3-(3,4-dichlorobenzyl)-8-thia-3-azabicyclo[3.2.1]octane-2,4-dione (VIIc) were prepared by the above method and are entered in Table I.

2-Carboxy-5-[N-(*p*-chlorobenzyl)carbamoyl]tetrahydrothiophene (VIIIb).—A mixture of IV (14.4 g, 0.09 mole) in ethanol (500 ml) containing KOH (5.1 g, 0.09 mole) was stirred for 30 min at room temperature, and the solution was evaporated to dryness *in vacuo*. The residue was dissolved in DMF (200 ml), and *p*-chlorobenzyl chloride (14.5 g, 0.09 mole) in DMF (50 ml) was added. The mixture was heated over a steam bath for 1 hr and stirred overnight at room temperature. The KCl was removed by filtration, and the filtrate was poured into 500 ml of $CHCl_3$ and diluted with water (1 l.). The $CHCl_3$ layer was separated, and the aqueous layer was extracted with two 150-ml portions of $CHCl_3$. The combined $CHCl_3$ extracts were washed successively with dilute NaOH, and two 100-ml portions of water, dried (Na_2SO_4), and evaporated to dryness *in vacuo*. The residue was recrystallized from methanol, then from methanol–water: yield 23.0 g (86%), mp 128.5–129.5°.

Anal. Calcd for $C_{13}H_{14}ClNO_3S$: C, 52.08; H, 4.70; N, 5.18. Found: C, 52.26; H, 4.90; N, 4.96.

2-Carboxy-5-[N-(benzyl)carbamoyl]tetrahydrothiophene (VIIIa, (mp 114.5–115.5° from ethanol) was obtained in 60% yield from

(6) Melting points were determined with the Thomas–Hoover capillary melting point apparatus and are corrected. Infrared spectra of the crystalline compounds were obtained from Nujol mulls with a Beckman IR-8 spectrophotometer. Analyses were performed by the Abbott Microanalytical Laboratory, North Chicago, Ill.

(7) Diborane gas was purchased from the Callery Chemical Co., Callery, Pa., and a 2.5% solution was made in tetrahydrofuran.

IV and benzyl chloride, by the method described for the preparation of VIIIb.

Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28; O, 18.09; S, 12.08. Found: C, 58.96; H, 5.79; N, 5.15; O, 18.30; S, 12.27.

2-(Carboxy)-5-[N-(3,4-dichlorobenzyl)carbamoyl]tetrahydrothiophene (VIIIc) was similarly obtained in 77% yield (mp 98.5–99.5° from methanol-water).

Anal. Calcd for $C_{13}H_{13}Cl_2O_3NS$: C, 46.71; H, 3.91; Cl, 21.21; N, 4.23. Found: C, 46.70; H, 3.91; Cl, 21.92; N, 4.23.

All the compounds in the VIII series had infrared absorption bands at 3330, 3160, 1730, and 1655–1635 cm^{-1}.

8-Thia-3-azabicyclo[3.2.1]octane-2,4-Dione 8,8-dioxide (IX).—A mixture of IV (4.0 g, 0.025 mole) and 30% H_2O_2 (3.6 ml) in glacial acetic acid (15 ml) was gradually heated to 70° and held at this temperature for 2 hr. On cooling slowly, white crystalline material (2.4 g, 50%) separated. Two recrystallizations from methanol gave the analytically pure IX: mp 284.5°; ν_{max} 3200, 3100, 1740, 1690, 1325, and 1170 cm^{-1}.

Anal. Calcd for $C_6H_7NO_4S$: C, 38.09; H, 3.72; N, 7.40; O, 33.83; S, 16.94. Found: C, 38.37; H, 3.66; N, 7.75; O, 33.70; S, 16.59.

Structure of Antibiotic C-73X[1]

ADORJAN ASZALOS, HERMAN HOBERECHT,[2] AND ALLEN I. COHEN

Squibb Institute for Medicinal Research, New Brunswick, New Jersey

Received October 23, 1966

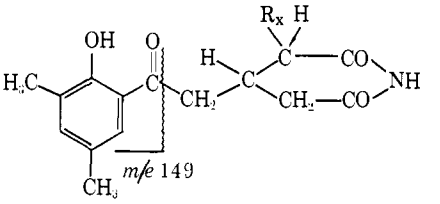
Three biologically active compounds have been isolated from the fermentation products of a strain of *Streptomyces griseus* originally obtained in a soil sample and included in the Culture Collection of the Squibb Institute for Medical Research (SC 3675). One compound was the previously identified actidione,[3] a second was the known antibiotic C-73[4] [3-(2-hydroxy-3,5-dimethylphenacyl)glutarimide], and a third, designated by the authors as C-73X, was found to be closely related to antibiotic C-73. Based on elemental analysis and ultraviolet, infrared, nmr, and mass spectra, the structure of C-73X is assigned as 2-hydroxy-3-(2-hydroxy-3,5-dimethylphenacyl)glutarimide. The procedure for isolation of C-73X is shown in Chart I.

The ultraviolet spectrum of C-73X showed two λ_{max}^{MeOH} values similar to those for C-73. Structural similarity of the two compounds was also demonstrable from the infrared, nmr, and mass spectra.

Relevant nmr spectral data for C-73, C-73X, and their acetates are shown in Table I. In addition to those proton resonances assignable to the structure of C-73, C-73X shows a resonance [τ 5.94, $(CD_3)_2SO$] attributable to a tertiary proton on a carbon atom to which is connected an electronegative atom. The acetylated derivative of C-73X likewise has a resonance attributable to the corresponding tertiary proton [τ 4.59, $CDCl_3$].

In the infrared spectrum, C-73X shows a band at 2.95 μ (KBr), indicating the presence of a hydroxyl group, in addition to those bands present in the infrared spectrum of C-73.

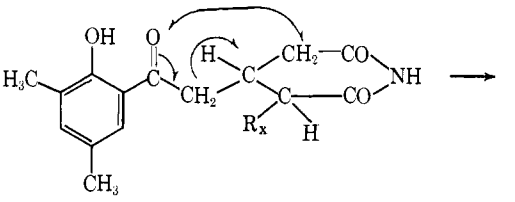
The mass spectra of C-73 and C-73X are shown in Figure 1. The parent ion (M^+) of C-73 appears at *m/e* 275. The M^+ of C-73X appears at *m/e* 291, leading us to conclude that C-73X is a hydroxylated derivative of C-73. The prominent (M − 18) peak at *m/e* 273 in the mass spectrum of C-73X suggests a facile dehydration of this compound. The most intense peak in the mass spectra of both compounds is at *m/e* 149, which suggests a fragment formed by cleavage of the bond to the aryl carbonyl (I).



I

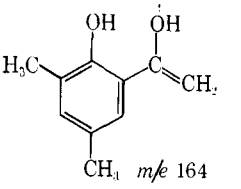
C-73, R_x = H
C-73X, R_x = OH

The peak at *m/e* 164 in the mass spectra of both compounds is attributable to the fragment formed by the proton rearrangement reaction shown below (II).

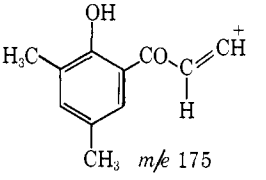


II

C-73, R_x = H
C-73X, R_x = OH



The peak at *m/e* 175, also shown by the mass spectra of both compounds, is probably attributable to the fragment formed in a proton rearrangement (III).



III

The intensity ratios for the peaks at *m/e* 164 and 175 are similar for both compounds. These similarities of intensity suggest that the part of the molecule between the aromatic ring and the glutarimide ring is the same in both compounds. Were the hydroxyl group in C-73X on the carbon α to the aryl carbonyl group, rather than on the carbon α to the imido carbonyl group, a significant change in the intensity ratio of the *m/e* 175 and 164 peaks from that found in C-73 might have been expected, arising from a different fragmentation process.

(1) This work was carried out as part of the effort on Cancer Chemotherapy National Service Center contract SA-43-ph-3041.

(2) Olin Mathieson Chemical Corp., New Haven, Conn.

(3) J. H. Ford and B. E. Leach, *J. Am. Chem. Soc.*, **70**, 1223 (1948).

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