TABLE I

ARYLOXYBIGUANIDE AND ARYLOXYGUANIDINE SALTS

Compound	Mp, °C	Yield, %	Recrystn solvent	Formula	Calcd, % C	Calcd, % H	Calcd, % Cl	Calcd, % N	Found, % C	Found, % H	Found, % Cl	Found, % N
Phenoxybiguanide hydrochloride (**2a**)	158–159	12	2-Propanol	$C_8H_{12}ClN_5O$	41.83	5.23	15.47	30.50	41.91	5.15	15.48	30.78
p-Tolyloxybiguanide nitrate (**2b**)	150–151	14	Methanol	$C_9H_{14}N_6O_4$	40.00	5.22		31.10	39.94	5.39		30.95
m-Chlorophenoxybiguanide nitrate (**2c**)	192–193	22	Ethanol	$C_8H_{11}ClN_6O_4$	33.05	3.79	12.22	28.92	32.65	4.08	12.49	29.22
Phenoxyguanidine hydrochloride (**3a**)	156–158	96	2-Propanol, ether	$C_7H_{10}ClN_3O$	44.80	5.33	18.93	22.40	45.01	5.45	18.90	22.50
m-Chlorophenoxyguanidine nitrate (**3b**)	149–150	24	2-Propanol, ether	$C_7H_9ClN_4O$	33.80	3.62	14.29	22.54	33.63	3.94	13.81	22.43

estimated as "reducing sugar" content by the method of Hoffman as modified for the Technicon Auto-Analyzer,[4] were not depressed significantly below controls when determined at 2 hr after dosing. For comparison, phenethylbiguanide hydrochloride effected a 50% lowering of blood sugar levels when administered at a dose of 50 mg/kg.[5]

Experimental Section[6]

Aryloxybiguanide Salts.—A solution of 0.02 mole of an aryloxyamine hydrochloride,[2,3] 0.02 mole of cyanoguanidine, and 40 ml of methanol was allowed to stand at room temperature for 4 days, and then concentrated under reduced pressure to an oily solid. For **2a**, the solid was recrystallized. For **2b** and **2c**, the crude solid was added to saturated aqueous sodium nitrate. The solid which then precipitated was recrystallized. Details are listed in Table I.

Aryloxyguanidine Salts.—A solution of 0.05 mole of an aryloxyamine hydrochloride[2,3] and 10 ml of 50% aqueous cyanamide[7] was allowed to stand overnight at room temperature. The solvent was distilled under reduced pressure, and the brown liquid residue was dissolved in warm 2-propanol. Addition of ether to the solution effected the separation of a solid (for **3a**) or a liquid (for **3b**). Addition of the liquid to saturated aqueous sodium nitrate gave a solid. Recrystallization gave the products; details are included in Table I.

(4) W. S. Hoffman, *J. Biol. Chem.*, **120**, 51 (1937).

(5) The animal testing was carried out by Drs. S. Riggi and D. Blickens of the Experimental Therapeutics Research Section of these laboratories.

(6) Melting points were determined in a Hershberg apparatus and are uncorrected. Microanalyses were performed by Mr. L. M. Brancone and staff.

(7) Aero® Cyanamide-50, American Cyanamid Co.

Reactions of Phenacyl Sulfides with Ammonia, Amines, and Hydrazines

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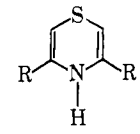
Our interest in 1,4-thiazines is derived from the parental relationship of these monocycles to the well-known and psychopharmacologically active phenothiazines and from the fundamental chemical nature of these little studied materials. Our attention was turned to 1,5-diketo sulfides with the thought that they would be easily accessible starting materials for convenient routes into the 1,4-thiazine system.

(1) Alfred P. Sloan Research Fellow.

Few attempts to accomplish condensation between 1,5-diketo sulfides and ammonia or amino compounds have been recorded and results, whether successful or unsuccessful, often appear ambiguous. In this paper we wish to report some structural clarifications and extensions of previous studies employing phenacyl sulfide and phenacyl sulfone as starting materials in the synthesis of 1,4-thiazines and related compounds.



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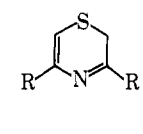
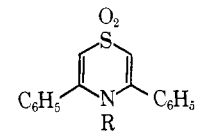


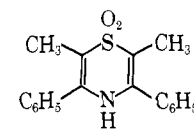
II

a, R = C_6H_5
b, R = H

Fujii[2] reported the synthesis of 3,5-diphenyl-1,4-thiazine by the condensation of phenacyl sulfide with ammonia; structure Ia was suggested for the product. We have repeated this preparation and found compelling evidence for the alternate structure IIa. The infrared spectrum is devoid of N–H absorption and the nmr spectrum shows, in addition to ten aromatic protons, a one-proton singlet at δ 6.28 (vinyl) and a two-proton singlet at δ 3.27. Such a structure has been previously proposed for the parent 1,4-thiazine (IIb).[3] This proposal, which was based on the failure of the compound to give a sulfonamide, has yet to be confirmed.



IIIa, R = H
b, R = CH_3
c, R = C_2H_5
d, R = $C_6H_5CH_2$
e, R = *n*-C_4H_9
f, R = CH_3OOCCH_2



IV

Baliah and Rangarajan[4] reported the formation of 3,5-diphenyl-4H-1,4-thiazine 1,1-dioxide (IIIa) by the condensation of phenacyl sulfone with ammonia in glacial acetic acid. The structure assignment was based on the observation that this compound underwent what was believed to be N-methylation by methyl

(2) K. Fujii, *J. Pharm. Soc. Japan*, **77**, 359 (1957); *Chem Abstr.*, **51**, 12103 (1957).

(3) C. Barkenbus and P. S. Landis, *J. Am. Chem. Soc.*, **70**, 684 (1948).

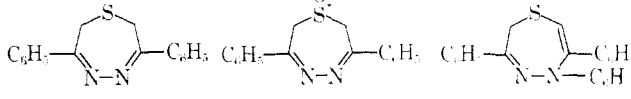
(4) V. Baliah and T. Rangarajan, *J. Org. Chem.*, **26**, 970 (1961).

iodide in the presence of potassium carbonate; no attempt was made to eliminate the possibility of C-methylation at position 2 or isomerization prior to N-methylation. The infrared and nmr spectra of IIIa obtained in our laboratory confirm the earlier structural assignment. The N–H band at 3400 cm^{-1} in the infrared spectrum of IIIa is not present in that of the methylated compound IIIb, thus also confirming the proposed N-alkylation. We have also prepared and examined other N-alkylated products (IIIc–f) of IIIa.

Methylation of phenacyl sulfone with methyl iodide in the presence of sodium ethoxide gave the symmetrical dimethyl derivative which upon refluxing with ammonium acetate in acetic acid afforded 2,6-dimethyl-3,5-diphenyl-4H-1,4-thiazine 1,1-dioxide (IV).

The change in position of the double bond with the state of oxidation of the sulfur in these thiazines is not well understood. Electron delocalization is perhaps more efficient in structures of type II than in type I since conjugation through sulfur in the latter is probably limited by the puckered nature of the ring. In view of this structural dissimilarity, the structure of the corresponding sulfoxide would be of interest. Oxidation of phenacyl sulfide with 1 equiv of *m*-chloroperbenzoic acid gave the known phenacyl sulfoxide.[5] Because of the instability of this compound or of the condensation product, it was impossible to obtain the desired 3,5-diphenyl-1,4-thiazine 1-oxide.

In confirmation of previous reports[2,4] no N-alkyl-1,4-thiazine derivatives were obtained when either phenacyl sulfide or sulfone was treated with a variety of primary amines under various conditions. The possibility that N-alkyl-1,4-thiazines might be obtained by $LiAlH_4$ reduction of the corresponding sulfones has also been investigated. It was found, as might be anticipated, that the double bonds were preferentially reduced leaving the sulfone grouping intact.



V VI VII

The reaction of phenacyl sulfide with hydrazine gave a product whose melting point and analysis were similar to those reported by Fromm and Ehrhardt.[6] The nmr spectrum confirmed the proposed structure 2,7-dihydro-3,6-diphenyl-1,4,5-thiadiazepine (V). It exhibited an AB pattern in the aliphatic region with doublets centered about δ 3.30 and 3.68 (J = 12.3 cps) as might be expected from the puckered nature of the ring. The 1,1-dioxide derivative (VI) was obtained by condensation of phenacyl sulfone with hydrazine and by oxidation of V by 2 equiv of *m*-chloroperbenzoic acid. Compounds V and VI undergo rather facile thermal decompositions to yield 3,6-diphenylpyridazine; these and related ring contractions have been observed independently by other workers.[7]

The reaction between phenacyl sulfone and phenylhydrazine under the conditions specified by Fromm and Flaschen for the formation of the seven-membered ring compound VII in our hands afforded only the monophenylhydrazone. Alternative reaction conditions gave identical results. Several other monophenylhydrazones were prepared. The following procedures were uniformly unsuccessful in providing cyclized products from these monophenylhydrazones: refluxing in acetic acid, acetic anhydride, pyridine, benzene, xylene, and chloroform with and without addition of a catalytic amount of organic or mineral acid. Under less drastic conditions the starting hydrazones were recovered while under the more drastic conditions decompositions took place. In similar reactions with hydroxylamine we were able to obtain only oximes.

Pharmacology. Gross symptomatologic characterizations employing male albino mice of the Swiss-Webster strain (20–30 g) were performed on 4-methyl-3,5-diphenyl-1,4-thiazine 1,1-dioxide (IIIb) and 2,7-dihydro-3,6-diphenyl-1,4,5-thiadiazepine (V). The compounds were administered orally in doses ranging from 100 to 1000 mg/kg. No appreciable pharmacotoxic signs were observed at any dosage level administered.

Experimental Section[8]

Phenacyl Sulfone (2,2′-Thiobisacetophenone S,S-Dioxide).—A cooled solution of 13.5 g (0.05 mole) of phenacyl sulfide in 40 ml of $CHCl_3$ was treated slowly with a solution of 21.0 g (0.7-g excess) of 85% *m*-chloroperbenzoic acid in 70 ml of ethanol. Thirty minutes after the addition was complete, the precipitate was filtered, washed thoroughly with cold methanol, and dried yielding 10.0 g, mp 120–121° (lit.[5] mp 120°). Careful cooling of the mother liquor afforded a second crop of 1.3 g raising the yield to 13.3 g (89%).

Phenacyl Sulfoxide.—A solution of 10.2 g (0.05 mole) of 85% *m*-chloroperbenzoic acid in 120 ml of $CHCl_3$ was added dropwise to a cooled and stirred solution of 13.5 g (0.05 mole) of phenacyl sulfide in 40 ml of $CHCl_3$. After the addition was complete the reaction mixture was transferred to a separatory funnel and washed twice with 5% $NaHCO_3$ and then with water. The $CHCl_3$ solution was dried ($MgSO_4$), the solvent was removed under diminished pressure, and the crude material was recrystallized from methanol yielding 10.2 g (71%), mp 111–113° (lit.[2,5] mp 113–115°, 98°).

3,5-Diphenyl-4H-1,4-thiazine 1,1-Dioxide (IIIa).—A mixture of 1.5 g (0.005 mole) of phenacyl sulfone and 1.2 g (0.02 mole) of urea in 15 ml of glacial acetic acid was heated under reflux for 18 hr. After cooling, the precipitated solid was filtered and recrystallized from ethanol; yield 1.2 g (90%) of colorless needles, mp 276–277° (lit.[4] mp 270–272°); selected infrared maxima (Nujol), 3380 (N–H) and 1100 cm^{-1} (SO_2).

Anal. Calcd for $C_{16}H_{13}NO_2S$: C, 67.81; H, 4.62. Found: C, 67.77; H, 4.73.

4-Alkyl-3,5-diphenyl-4H-1,4-thiazine 1,1-Dioxides (IIIb–f).—In a flask were placed 2.5 mmoles of 3,5-diphenyl-4H-1,4-thiazine 1,1-dioxide, 50 ml of dry acetone, 10–50 mmoles of alkyl halide, and 4 g of anhydrous K_2CO_3 in this order. After refluxing 12–24 hr, the hot solution was filtered, the acetone was removed, methanol was added, and the precipitate was filtered and recrystallized from ethanol (Table I).

The nmr spectrum of the 4-methyl derivative (IIIb) in (CD_3)$_2$CO showed singlets at δ 2.90 (3 H), 5.95 (2 H), and 7.45 (10 H); infrared ($CHCl_3$) selected bands: 3065, 3010, 1615, 1388, 1105 and 692 cm^{-1}. The 4-ethyl derivative (IIIc) exhibited similar bands at 3040, 3000, 1620, 1285, 1110, and 700 cm^{-1}.

2,2′-Thiobispropiophenone S,S-Dioxide.—A solution of 2.3 g (0.1 g-atom) of Na in 50 ml of absolute ethanol was added slowly to a stirred mixture of 6.0 g (0.02 mole) of phenacyl sulfone and

(5) E. Fromm and J. Flaschen, *Ann.*, **394**, 310 (1912).
(6) E. Fromm and A. Ehrhardt, *Ber.*, **54B**, 187 (1921).
(7) J. D. Loudon and L. B. Young, *J. Chem. Soc.*, 5496 (1963).

(8) Melting points were taken in open glass capillaries and are uncorrected. Microanalyses are by Midwest Microlab, Inc., Indianapolis, Ind. Infrared spectra were measured on a Perkin-Elmer Model 137-B spectrophotometer, and nmr spectra on a Varian Model DP-60 spectrometer, $(CH_3)_4Si$ as internal standard.

TABLE I

4-ALKYL-3,5-DIPHENYL-4H-1,4-THIAZINE 1,1-DIOXIDES

Compd	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
IIIb	70	228–230[a]	$C_{17}H_{15}NO_2S$				
IIIc	64	252–254	$C_{18}H_{17}NO_2S$	69.42	5.50	69.57	5.57
IIIe	71	205–206	$C_{20}H_{21}NO_2S$	70.76	6.23	70.64	6.49
IIId	48	242–243	$C_{23}H_{19}NO_2S$	73.96	5.13	74.07	5.36
IIIf	75	222–223	$C_{19}H_{17}NO_4S$	64.20	4.82	64.09	4.84

[a] Lit.[4] mp 224–226°.

TABLE II

DERIVATIVES OF PHENACYL SULFIDE AND PHENACYL SULFONE

Compd	Mp, °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Remarks
Phenacyl sulfide mono-*p*-nitrophenylhydrazone	213–213.5	$C_{22}H_{19}N_3O_3S$	65.16	4.73	64.94	4.69	Yellow needles
Phenacyl sulfone mono-*p*-nitrophenylhydrazone	211.5–212.5	$C_{22}H_{19}N_3O_5S$	60.26	4.37	60.21	4.49	Yellow needles
Phenacyl sulfone monophenylhydrazone	197–198[a]	$C_{22}H_{20}N_2O_3S$	67.34	5.10	67.08	5.36	Colorless needles[a]
Phenacyl sulfone dioxime	217–217.5[b]	$C_{16}H_{16}N_2O_4S$	57.80	4.82	57.82	4.95	

[a] Lit.[5] yellow needles, mp 193°. [b] Lit.[5] mp 204°. Under identical conditions (NaOAc, EtOH, reflux) the previous workers obtained the so-called phenacyl sulfone dioxime anhydride, mp 167°; however, their analytical data varied considerably from theory.

14.2 g (0.1 mole) of CH_3I in 150 ml of absolute ethanol. After 4 hr the reaction mixture was heated to reflux and then allowed to cool to room temperature. The ethanol was partially removed (about two-thirds), and the precipitate was filtered and recrystallized from ethanol yielding 2.5 g (38%), mp 203–204° (lit.[5] mp 178°).

Anal. Calcd for $C_{18}H_{18}O_4S$: C, 65.43; H, 5.49; S, 9.71. Found: C, 65.36; H, 5.41; S, 9.68.

2,6-Dimethyl-3,5-diphenyl-4H-1,4-thiazine 1,1-Dioxide (IV).—A mixture of 1.65 g (0.005 mole) of the foregoing compound and 0.8 g (0.01 mole) of ammonium acetate in 10 ml of glacial acetic acid was heated under reflux 5 hr and cooled. The precipitated solid was filtered, washed with methanol, and recrystallized from ethanol to provide 1.2 g (77%) of colorless needles, mp 260–262°.

Anal. Calcd for $C_{18}H_{17}NO_2S$: C, 69.42; H, 5.50; N, 4.50; S, 10.30. Found: C, 69.25; H, 5.52; N, 4.40; S, 10.34.

Reaction of Phenacyl Sulfone with Benzylamine.—A mixture of 1.5 g (0.005 mole) of phenacyl sulfone and 0.8 g (0.0075 mole) of benzylamine in 10 ml of xylene was heated under reflux for 3 hr. Cooling afforded 0.15 g (12%) of IIIa. Mixture melting point and infrared spectra confirmed the identity.

Reduction of 4-Methyl-3,5-diphenyl-4H-1,4-thiazine 1,1-Dioxide.—A suspension of 0.5 g of this compound[4] and 0.2 g of $LiAlH_4$ (3:1 ratio) in 25 ml of anhydrous ether was stirred and heated under reflux for 2 hr. The cooled reaction mixture was shaken with 50 g of ice and water, the ethereal layer was separated and dried ($MgSO_4$), and the ether was removed. The infrared spectrum of the residual syrup (0.37 g) did not show the C=C band at 1620 cm^{-1}. The **picrate** of 4-methyl-3,5-diphenyl-thiomorpholine 1,1-dioxide was prepared and recrystallized from ethanol; poor yield, mp 225–226°.

Anal. Calcd for $C_{23}H_{22}N_4O_9S$: C, 52.07; H, 4.18. Found: C, 52.13; H 4.35.

Phenylhydrazones and oximes were prepared in acetic acid solution or in ethanol (Table II).

2,7-Dihydro-3,6-diphenyl,4,5-thiadiazepine (V).—Ten drops of acetic acid were added to a stirred mixture of phenacyl sulfide (1.35 g, 0.005 mole) and 0.25 g (0.0075 mole) of hydrazine in 30 ml of ethanol. The mixture was heated under reflux for 8 hr and then allowed to cool to room temperature. The crude material was filtered and recrystallized from ethanol to provide 1.05 g (79%) of colorless solid: mp 177–177.5° (lit.[6,7] mp 175°); selected infrared maxima ($CHCl_3$), 3050 and 3000 (CH), 1555 (C=N) and 1445 cm^{-1} ($-CH_2$); nmr, doublets centered about δ 3.30 and 3.68 (J = 12.3 cps).

Anal. Calcd for $C_{16}H_{14}N_2S$: C, 72.14; H, 5.30. Found: C, 72.35; H, 5.48.

2,7-Dihydro-2,7-dimethyl-3,6-diphenyl-1,4,5-thiadiazepine.—The same procedure as above was employed using 2,2′-thiobispropiophenone instead of phenacyl sulfide. Recrystallization from methanol gave colorless crystals, mp 182–183°, in 55% yield.

Anal. Calcd for $C_{18}H_{18}N_2S$: C, 73.42; H, 6.16. Found: C, 73.50; H, 6.32.

3,6-Diphenyl-2,7-dihydro-1,4,5-thiadiazepine 1,1-Dioxide (VI).—The same procedure as above for V was employed using phenacyl sulfone. Recrystallization from ethanol–benzene gave in 73% yield, fine colorless needles: mp 195–196° dec (lit.[6] mp 196°); selected infrared maxima, 1545 (C=N), 1320 and 1140 (SO_2), and 685 cm^{-1} (C—S). This compound was also obtained by oxidation of V by 2 equiv of *m*-chloroperbenzoic acid in $CHCl_3$. Mixture melting point and infrared spectra confirmed the identity.

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Steroidal 2,3-Epithiospirolactones

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Initial reports[1-3] by Cella and co-workers that steroidal 17-spirolactones possessed antialdosterone activity prompted a continuous stimulus to synthesize and evaluate many related derivatives. This work was in part culminated by the observation of Cella and Tweit,[4] as reported in 1959, that the 7α-acetylthio analog of 3-(17β-hydroxyandrost-4-en-3-on-17α-yl)propionic acid γ-lactone was a highly potent steroidal aldosterone antagonist.

(1) J. A. Cella and C. M. Kagawa, *J. Am. Chem. Soc.*, **79**, 4808 (1957).
(2) C. M. Kagawa, J. A. Cella, and C. G. Van Arman, *Science*, **126**, 1015 (1957).
(3) J. A. Cella, E. A. Brown, and R. R. Burtner, *J. Org. Chem.*, **24**, 743 (1959).
(4) J. A. Cella and R. C. Tweit, *ibid.*, **24**, 1109 (1959).