Tetrahydrothiophene 1,1-Dioxide Derivatives

H. ELDRIDGE FAITH, MARIE P. KAUTSKY, AND BENEDICT E. ABREU[1]

Research Department, Pitman-Moore Company, Division of The Dow Chemical Company, Indianapolis 6, Indiana

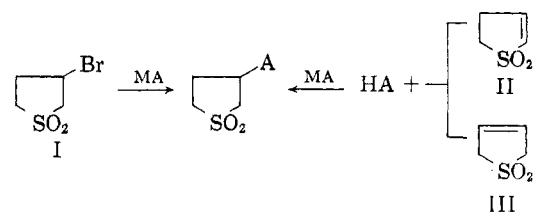
Received January 25, 1962

A number of derivatives of the cyclic sulfone, tetrahydrothiophene 1,1-dioxide, have been synthesized. Some of these may be classified as halides, acids, esters, basic ethers, basic esters, ketoamines, amines, and quaternary ammonium compounds. Several are related to known pharmaceutical compounds.

In the present investigation a variety of compounds have been made which contain the tetrahydrothiophene 1,1-dioxide or sulfolane ring. This grouping has been incorporated into a number of compounds structurally related to well known chemotherapeutic agents for the purpose of pharmacological and microbiological evaluation. Preliminary reports[2] from these laboratories have been made concerning the central nervous system stimulant action of 3-bromo- and 3-iodosulfolanes which antagonize pentobarbital depression and stimulate respiration. The ineffectiveness of some 3-alkylamino-, 3-alkylthio-, and 3-alkoxysulfolanes against experimental amebiasis, filariasis, schistosomiasis, and leishmaniasis has been reported,[3] as also have the analeptic and respiratory stimulant properties of 2,4-dimethylsulfolane.[4]

In Tables I and II the compounds described herein are tabulated in groups according to their chemical types and some miscellaneous ones are described in the Experimental. Compounds 14 and 34 are representative of replacement of a benzene ring by the sulfolane moiety in physiologically active phenoxyalkylamines and in phenylalkylamines, as for example, amphetamine. Compound 63 is an example of a phenobarbital-like structure wherein the phenyl group is replaced by sulfolane. This type of change (compound 48) was also made with one of the phenyl groups in the antispasmodic, adiphenine, a diphenylacetic acid ester of β-diethylaminoethanol. Another variation made in a compound of this latter type is represented by compound 27 in which carbon atoms 3 and 4 of the sulfone ring provide the two-carbon link between the oxygen and nitrogen atoms of the basic ester. This arrangement is also seen in the basic esters (24, 31) of the type represented by acetylcholine and procaine. A sulfolane substituted phenylpyrazolone (38) was also made.

3-Bromotetrahydrothiophene 1,1-dioxide, prepared by the action of phosphorus tribromide on the 3-hydroxy compound, was found to be useful in introducing the sulfolane group into various compounds. It was used to alkylate ethyl sodioacetoacetate and diethyl sodiomalonate in hot anhydrous alcoholic solution to yield the α-substituted esters (50,54). These same compounds and the phenylmalonic ester derivative (53) were prepared in better yields by the method of Kohler and Potter[5] by the addition of acetoacetic and the malonic esters under basic conditions in benzene to the α,β-unsaturated cyclic sulfone, 2,3-dihydrothiophene 1,1-dioxide, now prepared by dehydrobromination of the 3-bromo compound. A product identical to compound 50 was also obtained by the addition of diethyl malonate to 2,5-dihydrothiophene 1,1-dioxide, but in yield of 14% as compared to 87% when the 2,3-dihydro compound was used. The accompanying general diagram illustrates these three types of reactions.



M = Na except where MA = KCN. Reaction I: A = (a) $CH(COOEt)_2$, (b) $HC(COCH_3)COOEt$. Reaction II: A = (a), (b), (c) $C(C_6H_5)(COOEt)_2$, (d) CN. Reaction III: A = (b), (c) $OCH_2CH_2NR_2$ (R = Me, Et).

In the addition reaction II, two equivalents of ester (a, b, or c) and one of sodium were used. In two experiments with the reaction of phenylmalonic ester these proportions were changed, and it was found that low yields resulted when one fourth of an equivalent of sodium or when one equivalent of ester was used.

The position of the substituents (A) has not been determined definitely but position 3 has been assigned in accordance with numerous examples in the literature which indicate that the anionic portion of the addendum of these types attaches to the β-carbon atom in α,β-unsaturated esters, ketones, and sulfones[5,6] as exemplified in reaction II. Substitution in position 3 would seem to be likely in

(1) Present address: University of Texas Medical Branch, Galveston, Texas.

(2) L. C. Weaver, W. M. Alexander, B. E. Abreu, and G. R. Burch, *J. Pharmacol.*, **116**, 268 (1956); W. M. Alexander, B. E. Abreu, L. C. Weaver, H. E. Faith, and J. W. Newberne, *Arch. int. pharmacodyn.*, **CXIX**, 423 (1959).

(3) M. T. Leffler and W. D. Krueger, *J. Am. Chem. Soc.*, **71**, 370 (1949).

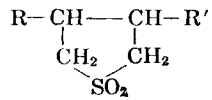
(4) W. A. McOmie, R. W. Pickering, and H. H. Anderson, *Fed. Proc.*, **6**, 357 (1947).

(5) E. P. Kohler and H. Potter, *J. Am. Chem. Soc.*, **57**, 1316 (1935).

(6) H. J. Backer and C. J. de Jong, *Rec. trav. chim.*, **70**, 377 (1951).

TABLE I

DERIVATIVES OF TETRAHYDROTHIOPHENE 1,1-DIOXIDE



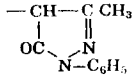
No.	R	R′	Yield, %	M.p.[a] or b.p. (mm.)	Formula	Calcd. C	Calcd. H	Calcd. Other[b]	Found C	Found H	Found Other[b]
1	Br[c]	H	38	46–47	$C_4H_7BrO_2S$	24.13	3.63	X 40.15	24.19	3.52	X 40.10
2	I	H	73	96–97	$C_4H_7IO_2S$			X 51.57			X 51.03
3	Cl	H	8	60.5–61	$C_4H_7ClO_2S$			X 22.93			X 22.87
4	Br	$(CH_3)_2NCOO$	71	122–123	$C_7H_{12}BrNO_4S$	29.38	4.24	X 27.93	29.40	4.31	X 27.73
5	CH_2CH_2Br	H	52	57–59	$C_6H_{11}BrO_2S$			X 35.19			X 35.29
6	4-$CH_3C_6H_5SO_3$	H	84	85.5–87	$C_{11}H_{14}O_5S_2$	45.50	4.86	S 22.09	45.33	4.83	S 22.12
7	CN	H	65	118–119	$C_5H_6NO_2S$	41.36	4.86	N 9.65	41.29	4.89	N 9.62
8	C(=NH)$NHCH_3$·HCl	H	77	224[d]	$C_6H_{13}ClN_2O_2S$	33.88	6.16		33.71	6.01	
9	C(=NH)$NHCH_3$·*p*-$CH_3C_6H_5SO_3H$	H		189–189.5	$C_{13}H_{20}N_2O_5S_2$	44.81	5.79	N 8.04	45.01	5.70	N 8.16
10	CH_2NH_2·HCl	H	78	238–239	$C_5H_{12}ClNO_2S$	32.34	6.52	N 7.55	32.58	6.74	N 7.54
11	CH_2NHCH_3·HCl	H	63	154–155	$C_6H_{14}ClNO_2S$	36.08	7.07	N 7.01	36.48	7.11	N 6.78
12	$CH_2CH_2NH_2$·HCl	H	87	180–182	$C_6H_{14}ClNO_2S$	36.08	7.07	N 7.01	36.09	7.49	N 6.68
13	$CH_2CH_2NHCH_3$·HCl	H	70	151–152.5	$C_7H_{16}ClNO_2S$	39.34	7.55		39.10	7.89	
14	$CH_2CH_2(NH_2)CH_3$·HCl	H	57	192–194	$C_7H_{16}ClNO_2S$	39.33	7.54	N 6.55	39.20	6.29	N 6.54
15	$CH_2CH_2N(C_2H_5)_2$·HCl	H	68	112–113	$C_{10}H_{22}ClNO_2S$	46.95	8.67		46.89	8.86	
16	$CH_2CH_2N(C_2H_5)_2$·C_2H_5I	H	52	213–215	$C_{12}H_{26}INO_2S$	38.40	6.98		37.98	8.83	
17	$CH_2CH_2NH(i\text{-}C_3H_7)$·HBr	H	92	166–167	$C_9H_{20}BrNO_2S$	37.76	7.04		38.14	7.24	
18	$NHCH_3$·HCl	HO	49	232–233[d]	$C_5H_{12}ClNO_3S$	29.78	5.50		29.96	5.60	
19	$N(CH_3)_2$·HCl[e]	HO	71	173–175[d]	$C_6H_{14}NO_3SCl$	33.42	6.55	N 6.50	33.58	6.44	N 6.42
20	$N(CH_3)_2$·CH_3I[f]	HO	85	208[d]	$C_7H_{16}INO_3S$			X 39.52			X 39.85
21	$NHCH_2CH_2OH$·HCl	HO	54	200–201	$C_6H_{14}ClNO_4S$			N 6.05			N 6.25
22	$NH(COCH_3)CH_2CH_2OCOCH_3$	CH_3COO	46	104–105	$C_{12}H_{19}NO_7S$	44.86	5.96	N 4.36	44.81	6.00	N 4.40
23	$N(CH_3)_2$·HCl[g]	CH_3COO	85	174–176	$C_8H_{16}ClNO_4S$	37.28	6.26		37.52	6.21	
24	$N(CH_3)_2$·CH_3I	CH_3COO	82	205–206[d]	$C_9H_{18}INO_4S$	29.76	5.00	X 34.94	29.93	5.00	X 35.01
25	$N(CH_3)_2$[h]	$(C_6H_5)_2CHCOO$	65	104–106	$C_{20}H_{23}NO_4S$	64.32	6.21		63.85	5.94	
26	$N(CH_3)_2$·HCl	$(C_6H_5)_2CHCOO$	64	188–190[d]	$C_{20}H_{24}ClNO_4S$	58.59	5.90		58.28	5.94	
27	$N(CH_3)_2$·$(COOH)_2$	$(C_6H_5)_2CHCOO$		152–154	$C_{22}H_{25}NO_8S$[i]	55.92	5.55		56.34	5.07	
28	$N(CH_3)_2$·$(CH_3)_2SO_4$	$(C_6H_5)_2CHCOO$	87	181–182[d]	$C_{22}H_{29}NO_8S_2$	52.89	5.85		52.56	5.74	
29	$N(CH_3)_2$[j]	*p*-$NO_2C_6H_5COO$		136–137	$C_{13}H_{16}N_2O_6S$	47.55	4.91		47.67	4.78	
30	$N(CH_3)_2$·HCl	*p*-$NO_2C_6H_5COO$	85	213[d]	$C_{13}H_{17}ClN_2O_6S$	42.80	4.70		42.80	4.34	
31	$N(CH_3)_2$·HCl[k]	*p*-$NH_2C_6H_5COO$	79	215–216[d]	$C_{13}H_{19}ClN_2O_4S$	46.61	5.72	N 8.37	46.55	5.72	N 8.48
32	$N(CH_3)_2$·HCl	$(CH_3)_2NCOO$	66	207–209[d]	$C_9H_{19}ClN_2O_4S$	37.69	6.68	N 9.77	37.65	6.25	N 9.75
33	$N(CH_3)_2$·CH_3I	$(CH_3)_2NCOO$	96	167–168[d]	$C_{10}H_{21}IN_2O_4S$			X 32.35			X 31.84
34	$OCH_2CH_2N(CH_3)_2$·HCl[l,m,n]	H	75	141–142[m]	$C_{14}H_{20}N_4O_{10}S$[n]	38.53	4.62	N 12.84	38.29	4.42	N 12.69
35	$OCH_2CH_2N(CH_3)_2$·CH_3I	H	95	153–154	$C_9H_{20}INO_3S$			X 36.34			X 36.50
36	$OCH_2CH_2N(CH_3)_2$·*n*-C_4H_9I	H	77	98	$C_{12}H_{26}INO_3S$			X 32.43			X 32.32
37	$OCH_2CH_2N(C_2H_5)_2$[o]	H	65	164–165(3)	$C_{16}H_{24}N_4O_{10}S$[p]	41.37	5.21	N 12.06	40.92	4.70	N 12.13
38		H	82	278–280	$C_{14}H_{16}N_2O_3S$	57.51	5.52	N 9.58	57.36	5.45	N 9.64

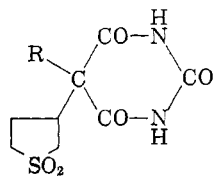
TABLE I (*Continued*)

No.	R	R′	Yield, %	M.p.[a] or b.p. (mm.)	Formula	Calcd. C	Calcd. H	Calcd. Other[b]	Found C	Found H	Found Other[b]
39	COOH	H	95	141–142	$C_5H_8O_4S$	36.57	4.91		36.59	5.00	
40	$CON(C_2H_5)_2$	H	86	100–101	$C_9H_{17}NO_3S$	49.29	7.81		49.30	7.69	
41	$COOCH_2CH_2N(C_2H_5)_2 \cdot HCl$	H	44	120–122	$C_{11}H_{22}ClNO_4S$	44.07	7.4		44.09	6.98	
42	$COOCH_2CH_2N(C_2H_5)_2 \cdot (COOH)_2$	H		71.5–72	$C_{13}H_{23}NO_8S$	44.18	6.56		44.40	6.44	
43	CH_2COOH	H	100	88–90	$C_6H_{10}O_4S$	40.44	5.66		40.44	5.80	
44	$CH_2COOC_2H_5$	H	87	184–187(5)	$C_8H_{14}O_4S$	46.59	6.84		46.42	6.56	
45	CH_2CH_2OH	H	32	200–204(5)	$C_{13}H_{14}N_2O_8S$[q]	43.57	3.94		43.52	4.19	
46	$CH(C_6H_5)COOH$	H	45	195–196	$C_{12}H_{14}O_4S$	56.67	5.55	S 12.61	56.71	5.39	S 12.52
47	$CH(C_6H_5)COOC_2H_5$	H	95	104–105	$C_{14}H_{18}O_4S$	59.55	6.42		59.50	6.08	
48	$CH(C_6H_5)COOCH_2CH_2N(C_2H_5)_2 \cdot (COOH)_2$	H	73	139–140	$C_{20}H_{29}NO_8S$	54.16	6.59		53.86	6.28	
49	$CH(COOH)_2$	H	96	166[d]	$C_7H_{10}O_6S$	37.84	4.86		37.82	4.88	
50	$CH(COOC_2H_5)_2$	H	66	65–66	$C_{11}H_{18}O_6S$	47.47	6.52		47.22	6.74	
51	$C(C_2H_5)(COOC_2H_5)_2$	H	76	57–58	$C_{13}H_{22}O_6S$	50.96	7.24		50.90	7.24	
52	$C(n\text{-}C_4H_7)(COOC_2H_5)_2$	H	51	70–71	$C_{15}H_{26}O_6S$	53.87	7.84		53.86	7.76	
53	$C(C_6H_5)(COOC_2H_5)_2$	H	67	60–62	$C_{17}H_{22}O_6S$	57.61	6.26		57.55	6.45	
54	$CH(COCH_3)COOC_2H_5$	H	61	103–105	$C_{10}H_{16}O_5S$	48.37	6.50		48.57	6.16	
55	CH_2COCH_3	H		43–44[r]	$C_{13}H_{16}N_4O_6S$[s]	43.81	4.53		43.60	4.91	
56	$CH_2CH(=NOH)CH_3$	H	68	110–112	$C_7H_{13}NO_3S$	43.96	6.84	N 7.33	43.82	6.22	N 7.37
57	$COCH_2Cl$	H	47	123–125	$C_6H_9ClO_3S$			X 18.03			X 17.78
58	COC_6H_5	H	14	99–100	$C_{11}H_{12}O_3S$	58.91	5.39		58.92	5.12	
59	$COCH_2N(C_2H_5)_2 \cdot (COOH)_2$	H	56	174–175[d]	$C_{12}H_{21}NO_7S$	44.57	6.55	N 4.33	44.54	6.24	N 4.36
60	$COCH_2N(C_2H_5)_2 \cdot CH_3I$	H	46	203[d]	$C_{11}H_{22}INO_3S$			X 33.82			X 33.85
61	$CH(OH)CH_2N(C_2H_5)_2 \cdot (COOH)_2$	H	96	96–98	$C_{12}H_{23}NO_7S$	44.29	7.12		44.30	6.55	

[a] See ref. 13. [b] Prefix indicates element analyzed, X = halogen. [c] See Experimental for the 2-bromo compound. [d] A number of compounds which melted with decomposition were inserted in melting point bath 3–5° below the melting point and heated 3° per min. [e] Ref. 9 reported the base. [f] Lit., m.p. 197–198° (ref. 9). [g] Ref. 9 reported the hydrobromide. [h] Lit., m.p. 100–101° (ref. 9). [i] Add $1/2$ H_2O. [j] Ref. 9 described two isomers, m.p. 151–152° and 216–217°. [k] Ref. 9 reported two isomeric bases. [l] Lit., m.p. 129–131° (ref. 9). [m] Hygroscopic hydrochloride. [n] Analyzed as the picrate, m.p. 147.5–148°. [o] Base previously reported (ref. 3). [p] Picrate, m.p. 78–80°. [q] 2,4-Dinitrobenzoate. [r] Ketone, not analyzed. [s] 2,4-Dinitrophenylhydrazone, m.p. 175–176°.

TABLE II

BARBITURATES SUBSTITUTED WITH TETRAHYDROTHIOPHENE 1,1-DIOXIDE



No.	R	Reaction time, hr.	Yield, %	M.p.,[a] °C.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
62	H	6.5	74	280	39.03	4.09	11.38	39.07	4.29	11.69
63	C_2H_5[b]	10	51[c]	322–324	43.79	5.15		43.66	5.40	
64	n-C_4H_9	11	33	253–255	47.67	6.00		47.70	6.06	
65	C_6H_5	12	45	319–320	52.17	4.38		52.54	4.22	

[a] See ref. 13. [b] One equivalent of sodium used. [c] 66%, calculating recovery of ester.

reaction I; however, dehydrobromination occurs under the basic conditions used, giving 2,3-dihydrothiophene 1,1-dioxide which can proceed by the addition reaction II. The yield of ester in reaction Ib was 29%, but when the reverse addition of sodioacetoacetic ester to an absolute ethanol solution of bromo compound was made for the purpose of keeping the mixture less basic, the dehydrobromination product, 2,3-dihydrothiophene 1,1-dioxide, was obtained. None of the ester (54) which would be expected from displacement of bromine was isolated.[7] In reaction III the β,γ-unsaturated sulfone under basic conditions forms a tautomeric mixture[8] containing the α-isomer, 2,3-dihydrothiophene 1,1-dioxide, which can react as indicated in reaction II.

A number of basic esters (no. 23–33) were made from the intermediate 4-dimethylamino-3-hydroxysulfolane[9] (19) which was obtained by reaction of 3,4-epoxytetrahydrothiophene 1,1-dioxide with dimethylamine. The epoxide, now prepared by the method of van Lohuizen and Backer,[10] had a melting point of 159–160° instead of the reported 130°[10] or 124.5–126°.[11] Recently its preparation by a different method has been reported (m.p. 159–160°)[12] and Loev[9] has found both high- and low-melting epoxides.

The 3-cyano derivative (7) was made in 43% yield by treating the 3-(p-toluenesulfonic) ester (6) with two equivalents of potassium cyanide in methyl ethyl ketone. The first observed step in the reaction was the elimination, within one hour, of p-toluenesulfonic acid which precipitated as the potassium salt. An almost quantitative yield of 2,3-dihydrothiophene 1,1-dioxide was obtained at this stage. In the resulting potassium cyanide–hydrogen cyanide–ketone–cyanhydrin mixture, hydrogen cyanide added to the unsaturated sulfone during the next arbitrarily chosen nine hours of refluxing. It was found that the nitrile could be produced in 65% yield from equal moles of the 2,3-dihydrothiophene 1,1-dioxide, methyl ethyl ketone cyanhydrin, and potassium cyanide. By this method, dissociation of the cyanhydrin provided a convenient source of hydrogen cyanide for the addition reaction. When either the basic potassium cyanide or the cyanhydrin was omitted from the process, no hydrogen cyanide addition occurred.

An additional report from these laboratories concerning the pharmacology of some of these compounds is planned.

Experimental[13]

3-Bromotetrahydrothiophene 1,1-Dioxide.[14]—To 72 g. (0.528 mole) of 3-hydroxytetrahydrothiophene 1,1-dioxide[15,16] in 150 ml. of anhydrous chloroform was added 52.5 g. of phosphorus tribromide in 15 ml. of chloroform at 10°. After this 30-min. addition the mixture was stirred for 4 hr. at 15 to 20° and allowed to stand at 25° for 16 hr. The solution was decanted from a sirupy layer; the latter was then extracted with chloroform. The chilled chloroform solution was washed with cold water, neutralized with an aqueous suspension of sodium bicarbonate, dried, and concentrated under reduced pressure to a sirup which was recrystallized from ether. Its solubility at 25° in water was about 4.5 g. per 100 ml. Distillation of the sirupy residue at 132° (2 mm.) yielded a less pure product.

3-Iodotetrahydrothiophene 1,1-Dioxide.—One hundred grams (0.502 mole) of dry 3-bromo compound was refluxed for 8.25 hr. in a solution of 83.0 g. (0.552 mole) of dry sodium iodide in 500 ml. of dry methyl ethyl ketone. The chilled

(7) The practically instantaneous neutralization of the reaction medium by hydrogen bromide elimination renders conditions unsuitable for subsequent addition by reaction II. There is a distinct possibility that under the more basic conditions normally used, reaction by displacement occurs in part.

(8)(a) E. de Roy van Zuydewijn, *Rec. trav. chim.*, **56**, 1047 (1937); (b) W. J. Bailey and E. W. Cummins, *J. Am. Chem. Soc.*, **76**, 1932 (1954).

(9) This compound and several derivatives noted in Table I were reported after the completion of this manuscript; *cf.*, Bernard Loev, *J. Org. Chem.*, **26**, 4396 (1961).

(10) O. E. van Lohuizen and H. J. Backer, *Rec. trav. chim.*, **68**, 1137 (1949).

(11) M. Prochaska and V. Horak, *Coll. Czech. Chem. Comm.*, **24**, 1509 (1959).

(12) W. R. Sorenson, *J. Org. Chem.*, **24**, 1796 (1959).

(13) Analyses were made by Dr. Carl Tiedcke, Laboratory of Microchemistry. Melting points and boiling points are uncorrected. Recrystallization solvents were absolute ethanol, 95% ethanol or dilute ethanol unless stated otherwise.

(14) We had no success in making this compound from the 3-hydroxy compound and hydrobromic acid or from 2,5-dihydrothiophene 1,1-dioxide and hydrogen bromide. Results similar to the latter have been reported by R. C. Krug, *et al.*, *J. Org. Chem.*, **23**, 212 (1958).

(15) Kindly supplied by Shell Development Co.

(16) H. J. Backer and J. Strating, *Rec. trav. chim.*, **62**, 815 (1943).

mixture was filtered and the crystals washed with water. Additional product was obtained by concentrating the organic filtrate and extracting with chloroform. Recrystallization from alcohol gave 90.2 g. of product.

This compound was also obtained in poor yield by the action of phosphorus triiodide on the 3-hydroxy compound.

2-Bromotetrahydrothiophene 1,1-Dioxide.[17]—A Grignard reagent was made from 3.96 g. of magnesium and 12.9 ml. of bromoethane in 180 ml. of anhydrous ether under nitrogen. To this was added 16.2 g. (0.135 mole) of redistilled tetrahydrothiophene 1,1-dioxide[15] in 250 ml. of dry benzene. The mixture was heated gradually and refluxed for 1.5 hr. Then 25.8 g. (0.323 g.-atom) of bromine was added to the mixture at room temperature and stirred for 2 hr. The solution was treated with sodium bisulfite solution and the benzene layer was extracted with water, dried, and concentrated under reduced pressure. The residue was distilled at 130–140° at 3 mm. pressure, giving an oil which was recrystallized from anhydrous ether containing some low boiling ligroin and then from carbon tetrachloride; yield, 4 g. As is characteristic of 2-halo sulfones the bromine atom was relatively unreactive, giving no bromide ions after 2.5 hr. of refluxing with methanolic potassium acetate or after 30-min. refluxing with alcoholic silver nitrate solution.

Anal. Calcd. for $C_4H_7BrO_2S$: C, 24.13; H, 3.54; Br, 40.14. Found: C, 24.06; H, 3.58; Br, 39.92.

3-Chlorotetrahydrothiophene 1,1-Dioxide.—Thirty grams of 3-hydroxytetrahydrothiophene 1,1-dioxide[15,16] reacted with 11 g. of phosphorus trichloride in 75 ml. of chloroform by the same procedure used in producing the 3-bromo compound (1). Fractionation of the final chloroform solution gave 5.5 g. of distillate at 132–135° (3 mm.). Extensive decomposition occurred above that temperature. Crystallization from ether gave 2.75 g. of compound. When heated with aqueous potassium acetate it yielded chloride ions. It was water-soluble.

Diethyl Tetrahydro-3-thiophenemalonate 1,1-Dioxide (50)—A. Eleven grams (0.479 g.-atom) of sodium was dissolved in 280 ml. of absolute ethanol. To the solution was added 77 g. (0.478 mole) of diethyl malonate. The 3-bromo compound (1), suspended as a melt in 150 ml. of warm absolute ethanol, was added by dropping funnel to the stirred, refluxing solution over a 1-hr. period. Refluxing was continued for 10 min. after the addition; then the neutral mixture was cooled, filtered to remove sodium bromide, and concentrated under reduced pressure. The residue was dissolved in 200 ml. of benzene, washed with water, and benzene and ethyl malonate were removed under reduced pressure, the pot temperature finally being raised to 135°. The residue was recrystallized from ether; yield 88.4 g.

B. By using 2,3-dihydrothiophene 1,1-dioxide[8a] (66) instead of 3-bromosulfolane, the yield was 43% by method A.

C. The same compound was obtained in 87% yield in benzene from 2,3-dihydrothiophene 1,1-dioxide and in 14% yield from 2,5-dihydrothiophene 1,1-dioxide[15] by the method used to prepare compounds 53 and 54.[19]

Diethyl α-Ethyltetrahydro-3-thiophenemalonate 1,1-Dioxide (51).—Diethyl (1,1-dioxo-3-tetrahydrothiophene)-malonate was ethylated with iodoethane in diethyl carbonate for 12.5 hr. at 90° by the method of Wallingford, *et al.*[18]

Diethyl α-Butyltetrahydro-3-thiophenemalonate 1,1-Dioxide (52).—This was made by a procedure similar to the one used above in producing the ethyl compound. After equal moles of the reactants had been stirred for 8 hr. at 95°, a 50% excess of 1-bromobutane was added and heating continued for a total of 24 hr.

Diethyl α-Phenyltetrahydro-3-thiophenemalonate 1,1-Dioxide (53).—To sodium granules (4.42 g., 0.192 g.-atom) in 50 ml. of xylene were added 600 ml. of anhydrous benzene and 90.8 g. of redistilled diethyl phenylmalonate. As the evolution of hydrogen subsided the mixture was heated with stirring at 50° for 2 hr. to dissolve most of the sodium. The addition of dry 2,3-dihydrothiophene 1,1-dioxide (66) (24.6 g., 0.208 mole) caused the remainder of sodium to dissolve. The solution was stirred at 45° for 3 days; then it was neutralized with hydrochloric acid, washed with water, and dried. Benzene and unchanged ester were removed by vacuum distillation, and the pot residue was recrystallized from anhydrous ether containing ligroin, giving 48 g. of product.

Ethyl α-Acetyltetrahydro-3-thiopheneacetate 1,1-Dioxide (54).—Condensation of acetoacetic ester with 2,3-dihydrothiophene 1,1-dioxide (66) (90 g.) was accomplished by the method used to prepare the phenylmalonate derivative (53). The product was recrystallized from absolute ethanol–ligroin mixture.

Its **2,4-dinitrophenylhydrazone** has a m.p. of 155–157°.

Anal. Calcd. for $C_{16}H_{20}N_4O_8S$: C, 44.86; H, 4.71. Found: C, 45.30; H, 4.78.

The ester was also obtained from 3-bromosulfolane in absolute alcohol by method A used in preparing the malonate (50); 29% yield. 2,3-Dihydrothiophene 1,1-dioxide was a by-product.

None of the ester (54) was obtained by the reverse addition of sodio acetoacetic ester to the bromo compound in absolute ethanol. The dehydrobromination product[7] (66) was obtained.

Experiments in the Preparation of Tetrahydro-3-thiophenecarbonitrile 1,1-Dioxide[20] (7).—A. 2,3-Dihydrothiophene 1,1-dioxide (66) (75.6 g., 0.64 mole) and 45.3 g. (0.69 mole) of finely ground potassium cyanide, both dried over concentrated sulfuric acid, were refluxed and stirred for 10 hr. with 71 g. (0.7 mole) of methyl ethyl ketone cyanhydrin[21] in 400 ml. of dry methyl ethyl ketone. Potassium cyanide was removed by filtration, and the solution acidified with acetic acid, chilled, and filtered to remove crystals. Concentration of the filtrate yielded additional crystals which were washed with water. There was obtained 61.1 g. of the carbonitrile which was recrystallized from absolute ethanol.[22]

B. 1,1-Dioxotetrahydro-3-thienyl *p*-toluenesulfonate (6) (5 g., 0.0172 mole) and 2.34 g. (0.036 mole) of finely ground potassium cyanide in 25 ml. of methyl ethyl ketone was processed as in experiment A to yield the nitrile in 43% yield. The use of a smaller amount (0.03 mole) of potassium cyanide gave a lower yield (35%).

C. In the reaction as described in experiment B, refluxing was stopped after 1 hr. The mixture was filtered and concentrated *in vacuo* to give an almost quantitative yield of 2,3-dihydrothiophene 1,1-dioxide and no nitrile.

D. Under conditions of experiment A except without potassium cyanide, no nitrile was obtained.

E. After 1.5 hr. of refluxing under conditions of experiment A, except without the cyanhydrin, a viscous precipitate formed. No nitrile was obtained.

Tetrahydro-3-thiophenecarboxylic Acid 1,1-Dioxide (39).—The nitrile (7) (61.1 g., 0.42 mole) was refluxed for 2.5 hr. in 300 ml. of 20% hydrochloric acid. Concentration of the solution to dryness *in vacuo* gave a solid which was dried over sodium hydroxide and separated from ammonium chloride by dissolving in hot acetone. Evaporation yielded 65.5 g. of white solid which was recrystallized from toluene–ethyl acetate solution.

Its acid chloride was made by heating 10 g. of the acid at

(17) This method of bromination has been applied to 2,3-dihydrobenzothiophene 1,1-dioxide; F. G. Bordwell and W. H. McKellin, *J. Am. Chem. Soc.*, **72**, 1985 (1950).

(19) For a similar reaction in the benzothiophene 1,1-dioxide series see ref. 17.

(18) V. H. Wallingford, M. A. Thorpe, and A. H. Homeyer, *ibid.*, **64**, 580 (1942).

(20) During this work, the preparation of this nitrile by the reaction of 2,3-dihydrothiophene 1,1-dioxide and hydrogen cyanide was reported (no yield given); P. Kurtz, *Ann.*, **572**, 23 (1951).

(21) W. J. Bailey, F. A. Naylor, and J. J. Hewitt, *J. Org. Chem.*, **22**, 1076 (1957).

(22) The use of an excess of cyanhydrin to possibly improve the yield was not tried.

90° for about 1.5 hr. in 37 ml. of thionyl chloride. Removal of thionyl chloride under reduced pressure yielded a product which melted at 87–89°. Recrystallization from dry benzene was accompanied with slight decomposition. The acid chloride lost hydrogen chloride in a desiccator at room temperature.

The N,N-diethylamide was made by treating the above acid chloride (9.15 g., 0.05 mole) with 7.35 ml. (0.1 mole) of diethylamine in 50 ml. of dry benzene at 80° for 1 hr.

Tetrahydro-3-thiophenemalonic Acid 1,1-Dioxide (49).—The malonic ester (50) (387.2 g., 1.39 moles) was refluxed for 1.5 hr. with 1800 ml. (4.48 moles) of 2.5 *N* sodium hydroxide solution. The chilled solution was gradually acidified with good stirring with an equivalent amount of hydrochloric acid (*d* 1.19). It was then concentrated to dryness under reduced pressure at 60°. The malonic acid was extracted with hot acetone and sodium chloride removed by filtration. Acetone was evaporated and the residue washed with ether to yield 296.7 g. of white crystals, m.p. 165°. A sample was recrystallized from ethyl acetate–ligroin mixture.

Tetrahydro-3-thiopheneacetic Acid 1,1-Dioxide (43).—Decarboxylation of 297 g. of the malonic acid (49) was accomplished by heating at 155° *in vacuo* with ground glass until carbon dioxide evolution ceased (2.25 hr.). An analytical sample was recrystallized from toluene–ethyl acetate solution without change in melting point.

The ethyl ester (44) was made by dissolving 238 g. of the acid in 1100 ml. of absolute ethanol, saturating with hydrogen chloride, and refluxing for 3 hr. The sirup obtained by concentrating the solution under reduced pressure was dissolved in ether, dried, and fractionally distilled, yielding 240 g. of product.

Tetrahydro-3-thiopheneëthanol 1,1-Dioxide (45).—The above ester (44) was reduced by the Bouveault-Blanc method in absolute ethanol.

Its 3,5-dinitrobenzoate was made in pyridine for analysis.

Tetrahydro-α-phenyl-3-thiopheneacetic Acid 1,1-Dioxide (46).—The corresponding diethyl malonate (53) (31.7 g., 0.089 mole) was refluxed for 2.5 hr. with 142 ml. (0.355 mole) of 2.5 *N* sodium hydroxide. The solution was cooled to 30–35° and acidified with an excess of hydrochloric acid (*d* 1.19). The solution effervesced and gave a gummy precipitate which was separated from the solution by decantation. It was boiled 10–15 min. with hot water containing some hydrochloric acid while effervescence continued, filtered and stirred as the filtrate cooled. Solidification was slow. An additional amount of product (about 50% more) was obtained by concentration of the filtrate and treating the concentrate with 71 ml. of 2.5 *N* sodium hydroxide as was originally done. The combined products were washed with ether to remove some impurities, and recrystallized from water; yield, 10.16 g. Acid hydrolyses of the malonate with 20% solutions of hydrogen chloride in water, dilute alcohol, or aqueous acetic acid were unsatisfactory.

The acid (46) was also obtained in quantitative yield by refluxing 1 g. of the ethyl phenylacetate derivative (47) for 3 hr. in 11 ml. of 20% hydrochloric acid.

Ethyl Tetrahydro-α-phenyl-3-thiopheneacetate 1,1-Dioxide (47).—The acid (46) (28.4 g.) was esterified by refluxing for 3 hr. in 190 ml. of absolute ethanol containing 33 g. of hydrogen chloride.

3,4-Epoxytetrahydrothiophene 1,1-Dioxide.—4-Bromo-3-hydroxytetrahydrothiophene 1,1-dioxide[23] could not be made satisfactorily by the reaction of 2,5-dihydrothiophene 1,1-dioxide in acetone with N-bromosuccinimide.[24] Accordingly the 4-bromo-3-acetoxy derivative[23] was made in yields of about 50% in glacial acetic acid by heating N-bromosuccinimide and 2,5-dihydrothiophene 1,1-dioxide for 2 hr. at 80–85°. Without recrystallization, the acetoxy derivative (100 g.) was hydrolyzed by boiling with 600 ml. of 10% hydrochloric acid for 20 min. and chilled; yield, 90%, m.p. 190–191°. The epoxide was obtained by a described procedure[10] from the hydroxy compound and barium carbonate; however, it melted at 159–160°; lit.,[10,11,12,9] 130°, 124.5–126°, 159–160°, 157–159°. It was recrystallized from ethanol or chloroform; yield, 67%.

Anal. Calcd. for $C_4H_6O_3S$: C, 35.81; H, 4.51. Found: C, 35.79; H, 4.19.

N-Substituted 4-Aminotetrahydrothiophene-3-ol 1,1-Dioxides.—The 4-dimethylamino compound (19) was prepared by treating 57 ml. of liquid dimethylamine with 2.5 g. (0.186 mole) of the above epoxide in a sealed pressure tube for 16 hr. at 25°, and then at 40° for 1 hr. The solid base was washed with several portions of warm benzene; the benzene washings were concentrated under reduced pressure, and the residue was washed with chloroform. Treatment of the base in alcohol with hydrogen chloride gave 30.5 g. of hydrochloride, m.p. 164–168°. Recrystallization from ethanol was not satisfactory for purification; therefore, it was acetylated by refluxing in 146 ml. of acetic anhydride for 55 min. to form the acetic acid ester (23) which was recrystallized from absolute ethanol (27.3 g.; 75% yield). Hydrolysis was effected by refluxing this for 15 min. in 149 ml. of 10% hydrochloric acid and concentrating *in vacuo* to dryness.

Its base melted 103–105° (no analysis).

The methiodide (20) was prepared from the base of compound 19 in chloroform at 40° for 24 hr. It was recrystallized from 65% ethanol.

The corresponding methylamino (18) and hydroxyethylamino (21) compounds were made from the epoxide by this method, omitting the esterification and hydrolysis steps.

The acetates (22,23) were made by refluxing the corresponding alcohols with five times their weight of acetic anhydride for 1 hr.

The methiodide (24) was made from the base of compound 23 in ethyl acetate with iodomethane at 25° for 20 hr. It was recrystallized from aqueous ethanol. A decomposition product from the ethanolic filtrate was identified by mixed melting point as 3-acetoxy-2,3-dihydrothiophene 1,1-dioxide.[10]

3-(2-Dimethylaminoethoxy)tetrahydrothiophene 1,1-Dioxide (34).—2,5-Dihydrothiophene 1,1-dioxide[15,25,26] (23.6 g., 0.2 mole) was stirred with 36.4 g. (0.4 mole) of 2-dimethylaminoethanol and 1.28 g. of 87% potassium hydroxide for 36 hr. at 25°. The reaction mixture was extracted with chloroform and fractionally distilled to give 23.5 g. of the product[27] at 162–165° (3 mm.) The hydrochloride was hygroscopic; therefore its picrate was analyzed.

The methiodide was made in dry benzene at 25° for 15 hr.

The *n*-butyl iodide was obtained from dry benzene after 2.5 days at 40°.

The ethiodide could not be obtained in crystalline form.

3-(2-Diethylaminoethoxy)tetrahydrothiophene 1,1-Dioxide (37).—This was obtained from 2-diethylaminoethanol by the method used in preparing the 2-dimethylamino derivative; b.p. lit.,[3] 175–181° (4 mm.). No crystalline hydrochloride was readily obtained; consequently the compound was analyzed as its picrate.

Its phosphate melted 130°; lit.,[3] 132–133°.

2-Diethylaminoethyl 1,1-Dioxotetrahydro-3-thiophenecarboxylate Hydrochloride (41).—To an anhydrous solution

(23) H. J. Backer, W. Stevens, and N. Dost, *Rec. trav. chim.*, **67**, 451 (1948); *Chem. Abstr.*, **43**, 558 (1949).

(24) Our heating time was 2.5 hr. as erroneously indicated in *Chem. Abstr.* (ref. 23) instead of 0.5 hr. as in the original article (ref. 23).

(25) O. Grummitt, A. E. Ardis, and J. Fick, *J. Am. Chem. Soc.*, **72**, 5167 (1950).

(26) R. C. Krug, G. R. Tichelaar, and F. E. Didot, *J. Org. Chem.*, **23**, 212 (1958).

(27) The same product was produced in similar yield from 2,3-dihydrothiophene 1,1-dioxide.

of 10.2 g. (0.087 mole) of 2-diethylaminoethanol in 30 ml. of benzene was added 20 ml. of pyridine. Then 17.1 g. (0.094 mole) of 1,1-dioxotetrahydro-3-thiophenecarboxylic acid chloride was added in 2-g. portions and stirred at 70° for 1.75 hr. A crude product precipitated by the addition of anhydrous ether crystallized when treated with absolute ethanol–ether. It was made basic in water with sodium bicarbonate, ether extracted, and treated with hydrogen chloride to yield the hydrochloride which was recrystallized from methyl ethyl ketone. It was hygroscopic.

The acid oxalate was made and recrystallized from methyl ethyl ketone.

4-Dimethylamino-1,1-dioxotetrahydro-3-thienyl Diphenylacetate Hydrochloride (26).—4-Dimethylaminotetrahydro-3-thiophene-ol 1,1-dioxide (10.66 g., 0.059 mole; m.p. 103–105°) from the hydrochloride (19) was heated at 100° for 1 hr. with 14.4 g. of diphenylacetyl chloride in 48 ml. of pyridine. Pyridine was removed by vacuum distillation and the residue was treated with sodium carbonate solution, dissolved in ether, and washed with water. Treatment of the dry ether solution gave the hydrochloride which was recrystallized from absolute ethanol; yield 15.5 g. It is acidic in water, partially precipitating soon as the free base.

The base, obtained by treating the hydrochloride with aqueous potassium carbonate and extracting with benzene, was recrystallized from 60% ethanol.

The acid oxalate from an ether solution of the base contained approximately 0.5 mole of water after recrystallizing from ethanol and drying over phosphorus pentoxide at 5 mm. pressure. Prior to drying it melted when inserted at 125°.

The metho methylsulfate (28) was prepared by warming the base with dimethyl sulfate at 35–40° in dry benzene for 24 hr. It was recrystallized from 98% ethanol with no change in melting point; however, after 4 hr. in water solution at 25° an acid-insoluble fraction (m.p. 123–124°) precipitated, probably because of loss of the amino function as evidenced by an amine odor in the filtrate.

4-Dimethylamino-1,1-dioxotetrahydro-3-thienyl N,N-Dimethylcarbamate Hydrochloride (32).—The alcohol (19) (30 g., 0.139 mole) was suspended in 95 ml. of dry triethylamine; 34 ml. of dimethylcarbamyl chloride was added and heated at 100° for 2.5 hr. The mixture was diluted with anhydrous ether, filtered to remove triethylamine hydrochloride, and the solution treated with hydrogen chloride to give the hydrochloride, which was recrystallized from absolute ethanol.

The methiodide was obtained by treating the base from the above hydrochloride in ethyl acetate with methyl iodide at 40°. It was recrystallized rapidly from absolute ethanol. When warmed in solvents it gave an amine odor.

4-Dimethylamino-1,1-dioxotetrahydro-3-thienyl *p*-Nitrobenzoate Hydrochloride (30).—The base of compound 19 (12.3 g., 0.069 mole) was dissolved in 74 ml. of dry pyridine and 13.6 g. (0.073 mole) of *p*-nitrobenzoyl chloride was added in portions. After heating at 100° for 1 hr., pyridine was removed under reduced pressure, the residue washed with ether, and recrystallized from 80% ethanol to yield 21.4 g. of the hydrochloride.

On standing in water solution a precipitate (m.p. 163–165°) gradually formed. Its separation into *p*-nitrobenzoic acid and the basic ester (29) below indicated a salt formation of the two, following gradual hydrolysis of the ester in water.

Its base (29), obtained by neutralization of the hydrochloride (30), was recrystallized from ethanol.

4-Dimethylamino-1,1-dioxotetrahydro-3-thienyl *p*-Aminobenzoate Hydrochloride (31).—The nitro compound (30) (5.0 g., 0.0137 mole) in 240 ml. of water was hydrogenated with 0.77 g. of 8% palladium chloride on carbon at 60 lb. pressure for 30 min.; yield, 3.6 g.

4-Bromo-1,1-dioxotetrahydro-3-thienyl N,N-Dimethylcarbamate (4).—4-Bromo-3-hydroxytetrahydrothiophene 1,1-dioxide[23,28] (10.0 g., 0.0465 mole) was heated for 2.5 hr. at 105° with 11.8 ml. of dimethylcarbamyl chloride. After the chloride was removed by vacuum distillation, the residue was suspended in ether and filtered. It was recrystallized three times from hexane containing some benzene; yield, 9.4 g.

1,1-Dioxo-2,3-dihydro-3-thienyl N,N-Dimethylcarbamate.—The above compound (4) (9.0 g.) was refluxed for 40 min. with 3.4 g. of potassium acetate in 30 ml. of methanol. The methanol was removed under reduced pressure after filtration and the residue was dissolved in chloroform, filtered, concentrated to dryness, and recrystallized from ether containing ligroin; yield, 3.98 g. (62%); m.p. 87–88.5°.

Anal. Calcd. for $C_7H_{11}NO_4S$: C, 40.96; H, 5.40; N, 6.83. Found: C, 40.29; H, 5.18; N, 6.74.

2-Diethylaminoethyl Tetrahydro-1,1-dioxo-α-phenyl-3-thiopheneacetate Acid Oxalate (48).—Sodium (0.92 g.) was treated with 45 ml. of dry 2-propanol. N,N-Diethyl-2-chloroethylamine hydrochloride (7.0 g., 0.0406 mole) and the acid (46) were added and refluxed for 8 hr. The hot mixture was filtered and the filtrate concentrated to a sirup. This was made alkaline with 10% sodium hydroxide solution, dissolved in ether, washed with water, and precipitated from the ether solution as the oxalate.

The base, which melted 67–68°, was not analyzed.

The methiodide (m.p. about 50°) was too hygroscopic for analysis.

3-(β-Bromoethyl)tetrahydrothiophene 1,1-Dioxide (5).—The β-hydroxyethyl compound (45) reacted with phosphorus tribromide for 2 hr. at 60° in dry chloroform. The product was recrystallized from absolute ether or water.

Preparation of Ethylamine Derivatives (12, 13, 17).—The β-bromoethyl compound (5) was allowed to stand with 60 to 70 equivalents of ammonia or appropriate amine in ethanol for 1 week. The hydrobromides so obtained, except compound 17, were converted to their bases and then to hydrochlorides.

N,N-Diethyl-β-(1,1-dioxotetrahydro-3-thiophene)ethylamine Hydrochloride (15).—The bromoethyl compound (5) (20 g., 0.088 mole) was heated at 65° with 45 ml. of diethylamine in dry benzene for 28 hr. Diethylamine hydrobromide was filtered, and the solution was concentrated *in vacuo*. The base was dissolved in anhydrous ether, filtered, and treated with hydrogen chloride. Recrystallization was from anhydrous ethyl acetate. It was hygroscopic.

The ethiodide was obtained from the amine in dry benzene after 5 days at 25°; yield, 52%. It was recrystallized from warm (35°) methanol.

1,1-Dioxotetrahydro-3-thiophenemethylamine Hydrochloride (10).—Ten grams (0.0688 mole) of the 3-carbonitrile[20] (7) in 120 ml. of acetic anhydride was reductively acetylated in a Paar hydrogenator at 25° in the presence of 0.2 g. of Adams' catalyst and 2 g. of 8% palladium chloride on carbon. After 11 hr. the anhydride was removed *in vacuo*, the residue warmed with ethanol, chilled, and filtered from 0.7 g. of starting nitrile. Removal of the ethanol left a sirup which was refluxed for 2.7 hr. with 32 ml. of 20% hydrochloric acid. Concentration of the solution yielded the hydrochloride (9.3 g.).

N-Methyl-1,1-dioxotetrahydro-3-thiophenemethylamine Hydrochloride (11).—The base of compound 10 was methylated by a method of Decker and Becker as modified by Woodruff.[29]

1-(1,1-Dioxotetrahydro-3-thienyl)-2-propanone (55).—The acetoacetic acid ester derivative (54) (112.5 g., 0.452 mole) was added with cooling to 628 ml. of 5% sodium hydroxide (0.785 mole) and stirred for 5.5 hr. at 25°. Decarboxylation was accomplished by adding 50% sulfuric acid to the solution at 45–50° over a 30-min. period and by con-

(28) Made as described in the above epoxide preparation.

(29) E. H. Woodruff, J. P. Lambooy, and W. E. Burt, *J. Am. Chem. Soc.*, **62**, 922 (1940).

tinuing the warming and stirring at pH 3 to 4 for 45 min. After neutralization with sodium bicarbonate, extraction of the solution with chloroform yielded the water-soluble ketone as an oil which eventually solidified (m.p. 43–44°, from anhydrous ether). It was analyzed as its 2,4-dinitrophenylhydrazone.

The oxime (56) was obtained from the above decarboxylation preparation by removing 270 ml. of water under reduced pressure and treating the ketonic solution with 38 g. of hydroxylamine hydrochloride and 48 g. of sodium acetate at 25° for 48 hr. Crystals were filtered from the chilled solution and washed sparingly with cold water; yield, 49 g. An additional 9.7 g. was obtained by extraction with chloroform. Recrystallization was from benzene. It gave a blue product with cobaltous chloride in chloroform characteristic of ketoximes.[30] With acidic 2,4-dinitrophenylhydrazine reagent it gave a 2,4-dinitrophenylhydrazone identical with that obtained from the ketone. The oxime hydrochloride melted 145–148°.

Tetrahydro-1,1-dioxo-α-methyl-3-thiopheneëthylamine Hydrochloride (14).—The oxime (56) (7.44 g., 0.0388 mole) was reduced in 200 ml. of boiling absolute ethanol by the addition of 238 g. of 3% sodium amalgam over a period of 1.75 hr. A total of 21 ml. of glacial acetic acid was added in portions to keep the mixture slightly acid during the reaction. The alcohol was removed under reduced pressure and the residual amine was extracted into chloroform and treated with hydrogen chloride. The amine from the purified hydrochloride distilled at 163° (3 mm.).

1,1-Dioxotetrahydro-3-thienyl *p*-Toluenesulfonate (6).—This ester was prepared by the reaction of 1,1-dioxotetrahydro-3-thiophene-ol[15] and *p*-toluenesulfonyl chloride in pyridine at 25° for 18 hr.

N-Methyl-1,1-dioxotetrahydro-3-thiophenecarboxamidine Hydrochloride (8).—Absolute ethanol (4.3 ml.) was added to 9 g. (0.062 mole) of the nitrile (7) in 225 ml. of anhydrous, purified dioxane and the chilled solution was saturated with anhydrous hydrogen chloride causing crystals to form. After 3.5 days in the refrigerator the imino ester hydrochloride was separated by filtration and dried over sodium hydroxide; yield, 14.1 g. It bubbled and resolidified at 120°, then melted at 158–160°. This (12.9 g.) was added to a chilled solution of absolute ethanol containing 2.6 g. of methylamine and allowed to stand for 3.5 hr. at 25°; the product was filtered from the suspension and recrystallized from absolute ethanol; yield, 9.2 g. It was hygroscopic.

The *p*-toluenesulfonic acid salt (9) was obtained in poor yield by fusion of the nitrile at 170° for 8 hr. with the methylamine salt of *p*-toluenesulfonic acid. It was converted to a hydrochloride identical to compound 8.

1,1-Dioxotetrahydro-3-thienyl Chloromethyl Ketone (57).—The acid chloride[31] of the 3-carboxylic acid derivative (12.0 g., 0.066 mole) in 75 ml. of dry chloroform was added dropwise to diazomethane (from 22.8 g., 0.221 mole of nitrosomethylurea)[32] in approximately 320 ml. of anhydrous ether at 0°. After standing at 0° for 4 hr. the mixture remained at 25° overnight. The ether–chloroform solution was decanted from a waxy product which was extracted with chloroform. The chloroform solution was filtered, chilled in an ice bath, and made acid with hydrogen chloride. The ether–chloroform solution was treated likewise and after the solutions were warmed to 30° they were concentrated *in vacuo*.

1,1-Dioxotetrahydro-3-thienyl Diethylaminomethyl Ketone Acid Oxalate (59).—The finely ground chloromethyl ketone (57) (17.2 g., 0.0875 mole) was added over a 30-min. period to 36 ml. (0.34 mole) of dry diethylamine in 300 ml. of anhydrous benzene at 70° and kept at 70° for 30 min. after the addition. Crystals were removed by filtration and the filtrate concentrated *in vacuo*. The basic residue was extracted into ether and treated with oxalic acid.

The methiodide was made by treating the free amine of the above compound with iodomethane in dry chloroform for 48 hr. at 25°.

α-(Diethylaminomethyl)tetrahydro-1,1-dioxo-3-thiophenemethanol Acid Oxalate (61).—The ketoamine (59) (5.7 g., 0.0177 mole) was hydrogenated in a solution of 40 ml. of ethanol and 28 ml. of water in the presence of 50 mg. of Adam's catalyst for 1 hr. The product was recrystallized from an absolute ethanol–ethyl acetate solution; yield, 5.5 g.

4-(1,1-Dioxotetrahydro-3-thienyl)-3-methyl-1-phenyl-5-pyrazolone (38).—The acetoacetic ester derivative (54) (5 g., 0.02 mole) was heated at 100° for 1.75 hr. with a mixture of 3 g. of phenylhydrazine hydrochloride, 2.4 g. of sodium bicarbonate, and 40 ml. of glacial acetic acid. After removal of the acetic acid *in vacuo* the residue was recrystallized from aqueous ethanol; yield, 4.84 g. It was soluble in dilute sodium hydroxide solution.

2-(Tetrahydro-3-thienyl)-2-phenylethyl 3,5-Dinitrobenzoate.—The ester (44) (0.02 mole) in ether was added over a 1-hr. period to 0.04 mole of lithium aluminum hydride in anhydrous ether and refluxed for 1.75 hr. After decomposition of the hydride with ethyl acetate and hydrochloric acid, the mixture was extracted with ether and benzene. The oil obtained was distilled at 185° (7–8 mm.); yield, 1.42 g. With 3,5-dinitrobenzoyl chloride in pyridine at 80° for 10 min. the alcohol gave 0.59 g. of the dinitrobenzoate, m.p. 97–99°. Analyses indicated that the sulfone group had been reduced to the sulfide.[33]

Anal. Calcd. for $C_{19}H_{18}N_2O_6S$: C, 56.71; H, 4.50; S, 7.96. Found: C, 56.52; H, 4.42; S, 7.69.

Isomer of 2,4-Dimethyl-2,5-dihydrothiophene 1,1-Dioxide.—When 2,4-dimethyl-2,5-dihydrothiophene 1,1-dioxide[15] (m.p. 41–42°) was heated 4 hr. at 65° with 2-dimethylaminoethanol in the presence of sodium hydroxide no basic ether was obtained; however, a neutral water-soluble product which reacted with potassium permanganate and with bromine was obtained; m.p. 50–51°. When mixed with the starting compound it melted at room temperature. These characteristics and the analysis indicated an isomer.

Anal. Calcd. for $C_6H_{10}O_2S$: C, 49.29; H, 6.90; S, 21.93. Found: C, 49.60; H, 6.86; S, 21.60.

1,1-Dioxotetrahydro-3-thienyl Phenyl Ketone (58).—To 0.038 mole of phenylmagnesium bromide in anhydrous ether was added 0.02 mole of anhydrous cadmium chloride. The mixture was refluxed for 45 min. and the ether was replaced with 35 ml. of dry benzene. To this was added finely ground 1,1-dioxotetrahydro-3-thiophenecarbonyl chloride[31] (7.0 g., 0.38 mole) in three portions. The mixture was stirred for 45 min. at 23°, then at 50° for 1 hr., allowed to stand overnight and continued for another hour at 50°. Treatment of the mixture with cold 10% sulfuric acid, extraction with benzene, and evaporation yielded a waxy product which was recrystallized from isopropyl alcohol. It formed a 2,4-dinitrophenylhydrazone, m.p. 226–228°.

2,3-Dihydrothiophene 1,1-Dioxide[8a] (66).—This was obtained by heating the 3-bromo compound (1) (150 g., 0.75 mole) with 0.82 mole of potassium acetate in 675 ml. of boiling methanol for 45 min. The mixture was cooled and filtered; the filtrate was concentrated *in vacuo*, diluted with benzene, and filtered again. Concentration of the filtrate gave a sirup which was crystallized from ether; yield, 90%; m.p. 50–52° (lit.,[8a,26] 48.5–49.5°; 49–50°).

Barbiturates.—These are listed in Table II. They were made in general by refluxing the appropriate malonic ester in

(30) W. Hieber and F. Leutert, *Ber.*, **60B**, 2310 (1927).
(31) Described in the preparation of compound 39.
(32) F. Arndt, *Org. Syntheses*, Coll. Vol II, 461 (1943).
(33) For similar reductions of cyclic sulfones see F. G. Bordwell and W. H. McKellin, *J. Am. Chem. Soc.*, **73**, 2251 (1951).

absolute ethanol with two equivalents of sodium ethoxide and two equivalents of urea.

Reaction of the *n*-butyl derivative (52) with thiourea yielded a sodium bicarbonate-soluble compound (m.p. 152–153°) which was possibly 5-*n*-butyl-2-thiobarbituric acid resulting from loss of 2,3-dihydrothiophene 1,1-dioxide from the molecule.

Anal. Calcd. for $C_8H_{12}N_2O_2S$: C, 47.98; H, 6.04; N, 13.99. Found: C, 47.98; H, 6.09; N, 14.25.

Acknowledgment.—We wish to express appreciation to Mrs. Ruth L. Shelley and Mr. Robert R. Smith for their aid in the developmental syntheses.

Some 2,5,8-Trimethyl-5,10-dihydrophenazasiline Derivatives

HENRY GILMAN AND ERNEST A. ZUECH

Chemical Laboratory of Iowa State University, Ames, Iowa

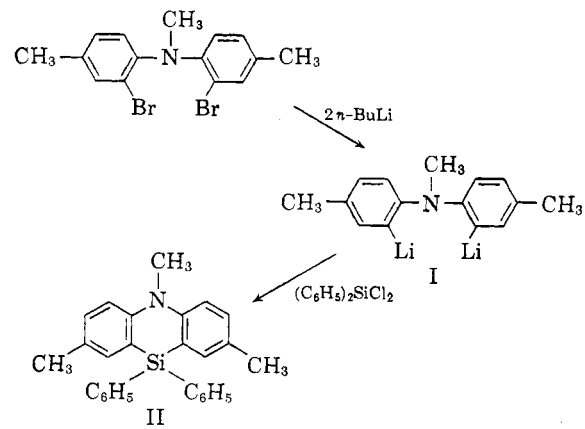
Received February 19, 1962

Bromination of *N*-methyldi-*p*-tolylamine gave *N*-methyl-2,2′-dibromodi-*p*-tolylamine in good yield. From the reaction of *N*-methyl-2,2′-dilithiodi-*p*-tolylamine and the appropriate halosilane, 2,5,8-trimethyl-10,10-diphenyl-5,10-dihydrophenazasiline, 2,5,8-trimethyl-10,10-dibenzyl-5,10-dihydrophenazasiline, 2,5,8,10,10-pentamethyl-5,10-dihydrophenazasiline, and 2,2′,5,5′,8,8′-hexamethyl-10,10′-spirobi[5,10-dihydrophenazasiline] were prepared. Reactions of the dilithium compound with *sym*-tetraphenyldisilane and with triphenylchlorosilane are also described.

The applicability and versatility of the cyclization reactions involving N-substituted 2,2′-dilithiodiarylamine derivatives and the appropriate halosilanes for the synthesis of 5,10-dihydrophenazasiline compounds have been previously demonstrated.[1,2] However, these procedures suffer because the required 2,2′-dibromodiarylamines are difficult to prepare and because N-alkylation has been accomplished only by reacting the corresponding N-lithio intermediates with alkyl sulfates in refluxing tetrahydrofuran.[1,2] The general interest in these nitrogen-containing heterocyclic silanes has prompted a search for simplified methods for their preparation. In a recent communication,[3] preliminary work was reported describing the synthesis of 5,10-dihydrophenazasiline compounds from di-*p*-tolylamine derivatives. This is a more thorough description of that work and includes several extensions.

Treatment of a glacial acetic acid solution of N-methyldi-*p*-tolylamine with two molar equivalents of bromine gave N-methyl-2,2′-dibromodi-*p*-tolylamine in a 61% yield. This same compound was also prepared from the known 2,2′-dibromodi-*p*-tolylamine[2,4] by reaction first with methyllithium and then with dimethyl sulfate in refluxing tetrahydrofuran. Subsequently, *N*-methyl-2,2′-dibromodi-*p*-tolylamine was converted to N-methyl-2,2′-dilithiodi-*p*-tolylamine (I) by halogen-metal interconversion with *n*-butyllithium and then to 2,5,8-trimethyl-10,10-diphenyl-5,10-dihydrophenazasiline (II) by treatment with diphenyldichlorosilane.

In an effort to obtain the dilithium compound I without the use of *n*-butyllithium, an ethereal



solution of N-methyl-2,2′-dibromodi-*p*-tolylamine was allowed to react with lithium metal. Treatment of this reaction mixture with diphenyldichlorosilane gave the 2,5,8-trimethylphenazasiline, compound II, but in a lower yield than that obtained above. Therefore, the method involving halogen-metal interconversion is preferred.

When two molar equivalents of N-methyl-2,2′-dilithiodi-*p*-tolylamine (I) were caused to react with silicon tetrachloride, 2,2′,5,5′,8,8′-hexamethyl-10,10′-spirobi[5,10-dihydrophenazasiline] was obtained in good yield. Likewise, treatment of the dilithium compound I with dimethyldichlorosilane and with dibenzyldichlorosilane gave 2,5,8,-10,10-pentamethyl-5,10-dihydrophenazasiline and 2,5,8-trimethyl-10,10-dibenzyl-5,10-dihydrophenazasiline, respectively.

In an attempt to prepare a seven-membered heterocyclic system, N-methyl-2,2′-dilithiodi-*p*-tolylamine (I) was allowed to react with *sym*-tetraphenyldisilane. However, scission of the silicon-silicon bond occurred and the only isolable product was 2,5,8-trimethyl-10,10-diphenyl-5,10-dihydrophenazasiline (II). Similar cleavages of

(1) H. Gilman and E. A. Zuech, *Chem. Ind.* (London), 1227, (1958); *J. Am. Chem. Soc.*, **82**, 2522 (1960).
(2) H. Gilman and E. A. Zuech, *J. Org. Chem.*, **26**, 3481 (1961).
(3) H. Gilman and E. A. Zuech, *ibid.*, **24**, 1394 (1959).
(4) H. Gilman and E. A. Zuech, *ibid.*, **26**, 2013 (1961).