The higher melting material was identified as the diketal **8**: ir ($CHCl_3$) 2940, 2830, 1680, 1380 cm^{-1}; nmr δ 3.38 (s, 12 H, OCH_3), 2.98 (s, 6 H, NCH_3); mass spectrum (160°) *m/e* 262 (M^+), 247 ($M^+ - CH_3$), 231 ($M^+ - OCH_3$), 216 ($M^+ - CH_3O$-CH_3), 203, 201, 190, 185, 157, etc.

The lower melting material was assigned structure **7**: ir ($CHCl_3$) 2940, 2830, 1702, 1340 cm^{-1}; nmr δ 3.40 (s, 6 H, OCH_3), 3.34 (s, 3 H, N_4CH_3), 3.05 (s, 3 H, N_1CH_3); mass spectrum (160°) *m/e* 216 (M^+), 201, 185, 157, 144, 142, 131, 116, 103, 88.

2,3,5,6-Tetraketo-1,4-dimethylpiperazine (9).—The appearance of a sample of **6** (40 mg), stored in an open flask for 2 weeks, changed drastically and the original big cubic crystals had become brittle and calcified. The material was now found to be insoluble in most organic solvents, but soluble in DMF, DMSO, water, acetic acid, and CF_3COOH. This material was subjected to vacuum sublimation [130° (0.4 mm)]; a sample of the sublimate on recrystallization from glacial acetic acid yielded rhomboid plates of dec pt 320° (sample rapidly sublimed around 270°). The rest of the sublimate was used for spectral analysis: ir (Nujol) 1695 cm^{-1} (br); nmr (CF_3COOH) δ 3.51 (s); mass spectrum (140°) *m/e* 170 (M^+), 142 ($M^+ - CO$), 114 ($M^+ - 2CO$), 113 ($M^+ - CONHCH_3$), 86 ($M^+ - 3CO$), 85 ($M^+/2$), 70, 58, 57, 56.

Anal. Calcd for $C_6H_6N_2O_4$: C, 42.36; H, 3.56; N, 16.47. Found: C, 41.91; H, 3.37; N, 16.58.

Registry No.—**1**, 35141-11-8; **3**, 35191-65-2; **6**, 35191-66-3; **7**, 35141-12-9; **8**, 35141-13-0; **9**, 35141-14-1; **11**, 10574-23-9.

The Preparation of Some 1,3,4,6-Tetrahydrothieno[3,4-*c*]pyrrole 2,2-Dioxides[1]

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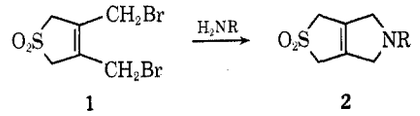
In a recent report,[3] it was indicated that, when 3,4-bis(bromomethyl)-2,5-dihydrothiophane 1,1-dioxide (**1**) was reacted with various amines even under



1 **2**

very mild conditions, in either protic or aprotic solvents, intractable mixtures were obtained. Only the weakly basic *p*-chloroaniline was reported to react with **1** over a 3-day period to yield the corresponding bicyclic pyrrolidine. We felt that it was important to report the successful preparation, without apparent difficulty, of several 1,3,4,6-tetrahydrothieno[3,4-*c*]pyrrole 2,2-dioxides (**2**) by the reaction of alkyl and aryl primary amines with the dibromo sulfone (**1**) in both protic and aprotic solvents. These reactions were completed, for the most part, in less than 2 hr.

Gschwend and Haider[3] had proposed that the difficulty with the reaction lay with the fact that the strongly acidic character of the sulfolene (**1**) protons toward the basic amine strongly favored proton abstraction and suppressed the nucleophilicity of the amines. Although we had earlier reported[4] that this abstraction process was predominant when strong nucleophiles such as hydroxides, sulfides, and alkoxides were reacted with **1**, this does not appear to occur to any great extent with those primary amines we have studied.

By reacting the dibromo sulfone (**1**) with aniline (pK_a 4.63) or *p*-anisidine (pK_a 5.34) in methanol (in the presence of anhydrous sodium carbonate, which neutralized the amine hydrobromide salts as they were formed), the corresponding bicyclic pyrrolidines were obtained in moderately good yields (38–78%). These reactions were complete in less than 2 hr, yielding white crystalline products which gave decomposition points and nmr and ir spectra similar to those obtained by Gschwend and Haider[3] for the *p*-chloroaniline derivative (Table I). In our preparation of the *p*-chloroaniline derivative, the reaction rate was so slow at room temperature under these conditions that the reaction mixture was heated at 55° for 1 hr.

TABLE I

AMINES REACTED WITH 3,4-BIS(BROMOMETHYL)-2,5-DIHYDROTHIOPHENE 1,1-DIOXIDE

Amine	pK_a[b]	Solvent	Reaction time, hr	% yield
Aniline	4.63	MeOH	2	38–74
p-Anisidine	5.34	MeOH	2	73–83
p-Chloroaniline[a]	4.15	MeOH	2	34
Benzylamine	9.33	CH_3CN	1	47–60
Methylamine	10.81	CH_3CN	1	37
Ethylamine	10.66	CH_3CN	1	32

[a] This was also prepared by Gschwend and Haider.[3] [b] "CRC Handbook of Chemistry and Physics," 50th Ed., Chemical Rubber Co., Cleveland, Ohio, 1969, pp 115–116.

The much stronger primary amines such as methylamine (pK_a 10.81) and ethylamine (pK_a 10.66) also gave reasonable yields of the corresponding bicyclic pyrrolidines with **1**. These amines reacted in acetonitrile to yield a mixture of bicyclic free amine and the corresponding HBr salt. The latter is treated with Na_2CO_3 to liberate the bicyclic amine product.

In contrast to the arylamine bicyclic pyrrolidines, which decomposed on heating, the alkyl compounds gave sharp melting points. Another difference between the alkylamines and the arylamines was that the former appeared to have a much faster reaction rate. The side products from both of these reactions, other than the corresponding primary amine hydrobromide salt, were intractable polymeric gums or oils.

Experimental Section[5,6]

5-Phenyl-1,3,4,6-tetrahydrothieno[3,4-*c*]pyrrole 2,2-Dioxide.—The dibromo sulfone[7] (3.04 g, 10 mmol) was dissolved in 200 ml of boiling methanol. Sodium carbonate (0.53 g) and 0.93 g (10

(1) This work was supported in part by the National Science Foundation Grant GP26616.

(2) A Texaco Fellow.

(3) H. W. Gschwend and H. Haider, *J. Org. Chem.*, **37**, 59 (1972).

(4) R. M. Ottenbrite, *Va. J. Sci.*, **21**, 196 (1970).

(5) Melting points were obtained in a Thomas–Hoover melting point apparatus and are uncorrected. Nmr spectra were recorded on a Varian A-60 instrument with TMS internal reference, and ir spectra were recorded on a Perkin-Elmer 337.

(6) We wish to thank Texaco, Inc., Research Laboratories, Richmond, Va., for the analytical analyses.

(7) G. B. Butler and R. M. Ottenbrite, *Tetrahedron Lett.*, 4873 (1967).

mmol) of aniline were added to the hot methanol solution. The mixture was stirred and allowed to cool, during which time all of the sodium carbonate was consumed (about (0.5 hr). Another 0.53-g portion of Na_2CO_3 was added to completely neutralize the amine hydrobromide being formed in the reaction. The reaction mixture was stirred for another 90 min, during which time all of the sodium carbonate was consumed and most of the bicyclic product precipitated. The reaction mixture was allowed to stand in a freezer overnight and the bicyclic product was recovered by filtration. Recrystallization from hot methanol yielded from 38 to 74% (dec pt 156–157°): ν^{KBr} 1580, 1490, 1370, 1287, 1188, 1111, 745, 686 cm^{-1}; nmr (CF_3COOD) δ 4.3 (s, 4 H), 5.02 (s, 4 H), 7.67 (s, 5 H); nmr ($CDCl_3$) δ 3.87 (s, 4 H), 4.19 (s, 4 H), 6.4–6.84 and 7.09–7.34 (broad phenyl absorption, 5 H).

Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5 95. Found: C, 61.77; H, 5.52; N, 5.83.

5-(*p*-Methoxyphenyl)-1,3,4,6-tetrahydrothieno[3,4-*c*]pyrrole 2,2-Dioxide.—The 5-(*p*-methoxyphenyl) product was prepared by a procedure similar to that described above: yield 73–83%; dec pt 156°; ν^{KBr} 2825, 1520, 1314, 1253, 1238, 1185, 1119, 1038, 811 cm^{-1}; nmr (CF_3COOD) δ 3.95 (s, 3 H), 4.26 (s, 4 H), 4.95 (s, 4 H), 7.16 and 7.59 (AB, J = 9 Hz, 4 H); nmr (DMSO-d_6), δ 3.67 (s, 3 H), 4.07 (broad peak, 8 H), 6.41 and 6.89 (AB, J = 9 Hz, 4 H).

Anal. Calcd for $C_{13}H_{15}NO_3Si$: C, 58.85; H, 5.69; N, 5.28. Found: C, 59.36; H, 5.58; N, 5.14.

5-(*p*-Chlorophenyl)-1,3,4,6-tetrahydrothieno[3,4-*c*]pyrrole 2,2-Dioxide.—This bicyclic pyrrole was obtained by following a procedure similar to that above, with the exception that the reaction mixture was held at 55° for 1 hr. Recrystallization from hot methanol yielded 0.8 g (34%), dec pt 153° (lit.[3] 153°).

5-Methyl-1,3,4,6-tetrahydrothieno[3,4-*c*]pyrrole 2,2-Dioxide.—The dibromo sulfone (12.11 g, 40 mmol) and 130 mmol of anhydrous methylamine in 300 ml of acetonitrile were stirred at room temperature for 60 min. The reaction mixture was filtered to remove the methylamine hydrobromide which precipitated, and the filtrate was evaporated to dryness. The residue was triturated in 100 ml of ether, and the ethereal solution was reduced in volume to 25 ml and allowed to stand in a freezer overnight; 1.1 g of the bicyclic product was obtained. The residue that remained after the ether washing was dissolved in methanol and neutralized with sodium carbonate. The methanol was removed under reduced pressure and the resultant residue was also triturated with 100 ml of ether. From this ether solution 1.5 g of the bicyclic product was obtained: total yield 2.8 g (37%); mp 89–90°; ν^{KBr} 1297, 1262, 1174, 1143, 1100, 848, 792 cm^{-1}; nmr (CF_3COOD) δ 3.37 (s, 3 H), 4.10–5.17 (s, 4.22 with broad AB pattern, 8 H; nmr ($CDCl_3$) δ 2.51 (s, 3 H), 3.56 (s, 4 H), 3.75 (s, 4 H).

Anal. Calcd for $C_7H_{11}NO_2S$: C, 48.53; H, 6.39; N, 8.08. Found: C, 48.92; H, 6.07; N, 7.95.

5-Ethyl-1,3,4,6-tetrahydrothieno[3,4-*c*]pyrrole 2,2-Dioxide.—The 5-ethyl product was prepared by the same procedure as the 5-methyl product. The only deviation from the procedure is that the ethylamine hydrobromide did not precipitate: 32%; mp 98–99°; ν^{KBr} 1285, 1264, 1184, 1154, 1166, 1100, 1032, 847, 793, 770 cm^{-1}; nmr (CF_3COOD) δ 1.52 (t, J = 7 Hz, 3 H), 3.64 (q, J = 7 Hz, 2 H), 4.06–5.04 (s, 4.18 with a broad AB pattern, 8 H); nmr ($CDCl_3$) δ 1.12 (t, J = 7 Hz, 3 H), 2.75 (q, J = 7 Hz, 2 H), 3.59 (s, 4 H), 3.80 (s, 4 H).

Anal. Calcd for $C_8H_{13}NO_2S$: C, 51.35; H, 6.98; N, 7.48. Found: C, 51.08: H, 6.76; N, 7.30.

5-Benzyl-1,3,4,6-tetrahydrothieno[3,4-*c*]pyrrole 2,2-Dioxide.—The 5-benzyl product was prepared by the same procedure as the 5-methyl product: 46–60%; mp 100°; ν^{KBr} 2780, 1298, 1263, 1110, 1091, 740, 700 cm^{-1}; nmr (CF_3COOD) δ 4.16 (s, 4 H), 4.37–4.77 (s, 4.69 and broad peak, 6 H), 7.57 (s, 5 H); nmr ($CDCl_3$) δ 3.60 (s, 4 H), 3.73 (s, 4 H), 3.86 (s, 2 H), 7.31 (s, 5 H).

Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.07; N, 5.62. Found: C, 62.63; H, 5.86; N, 5.38.

Registry No.—1, 18214-57-8; 2 (R = phenyl), 35105-69-2; 2 (R = *p*-methoxyphenyl), 35105-70-5; 2 (R = *p*-chlorophenyl), 32515-66-5; 2 (R = methyl), 35105-72-7; 2 (R = ethyl), 35105-73-8; 2 (R = benzyl), 35105-74-9.

The Preparation of 17β-Hydroxyestra-4,6-dien-3-one and Its Stereospecific β-Face Reduction at Carbons 6 and 7[1]

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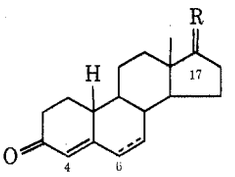
In connection with studies on the metabolism of 19-nor steroids we required estr-4-ene-3,17-dione (**1a**) labeled with a hydrogen isotope in a stable position. We decided to introduce the lable at C-7 by reducing 17β-hydroxyestra-4,6-dien-3-one (**1c**) with tris(triphenylphosphine)rhodium(I) chloride as was done in the steroidal C_{19} series.[2] Usual one-step procedures for the preparation of the diene starting material proved unsatisfactory. Reaction of chloranil (2,3,5,6-tetrachloroquinone) with estr-4-ene-3,17-dione or the corresponding 17β-hydroxy compound in refluxing *tert*-butyl alcohol gave a negligible yield of the desired $\Delta^{4,6}$-3-one compound, although the procedure gives reasonable results with C_{19} steroids.[3,4] Use of DDQ (dichlorodicyanoquinone) and acid catalysis was somewhat better, but was still unsatisfactory. Although the reaction goes to completion in 0.5 hr using a C_{19} compound,[5] only 75% of 17β-hydroxyestr-4-en-3-one (**1b**) was dehydro-



1a, R = O
b, R = 17β-OH, 17α-H
c, Δ^6-**1b**

genated in 1.5 hr and gave product mixtures that required extensive purification. However, we succeeded in obtaining complete reaction of 17β-hydroxyestr-4-en-3-one using chloranil in *tert*-butyl alcohol, ethanol, or methanol by heating to only 50° for 2–3 hr. The products were separated readily from the reagent materials by alumina column chromatography and further purification of the steroid fraction by tlc gave the pure $\Delta^{4,6}$-diene in good yield. A small amount of a mixture also was isolated and was tentatively identified as the phenolic ethyl ethers of estradiol-17β and the corresponding Δ^6 compound. This indicated that some C-1,2 dehydrogenation took place also and suggested that the same conditions, but with DDQ as oxidant, might bring about dehydrogenation at C-1 as occurs with testosterone, rather than at C-6 which occurs with 17β-hydroxyestr-4-en-3-one (19-nortestosterone).[6] How-

(1) (a) An outline of portions of this work has appeared in a communication: H. J. Brodie and C. E. Hay, *Biochem. J.*, **120**, 667 (1970). (b) Supported by U. S. Public Health Service, NIH Grants AM 14625, AM 6894, and GM 16928.

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