Experimental Section

Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Melting points were taken on a Fisher-Johns melting point apparatus and are corrected. Ir spectra were taken on a Perkin-Elmer 337 spectrophotometer. Nmr spectra were obtained with a Varian A-60 spectrometer in $CDCl_3$ at a concentration of 10% with TMS as an internal reference. Mass spectra were obtained on an Associated Electrical Industries MS902 Double Focusing High Resolution Mass Spectrometer equipped with a Honeywell 7600 Frequency Modulated Analog Tape Reader. The spectra were run at 70 eV. Chromatogram strips (K301R) were used for tlc, and the spots were detected with uv light.

1-(*p*-Iodobenzenesulfonyl)-3,5-di-*n*-propyl Isocyanurate (1).—A solution of 0.5 g (0.0018 mol) of *p*-iodobenzenesulfonamide in 5 ml (0.052 mol) of *n*-propyl isocyanate and 0.1 ml of triethylamine was refluxed with stirring for 96 hr. The excess *n*-propyl isocyanate and triethylamine were removed and the residue was dissolved in 15 ml of ethyl acetate. The ethyl acetate solution was filtered and 5 g of silica gel (80–200 mesh) was added to the filtrate. The ethyl acetate was removed *in vacuo* and 50 ml of benzene was added to the resin and evaporated *in vacuo* to remove the last traces of ethyl acetate. The dried silica gel with the reaction mixture adsorbed on it was added to the top of a silica gel column (60 × 2.5 cm), and the column was eluted with benzene at a rate of 4 ml/min. The product was eluted in the fractions between 500 and 600 ml. Aliquots of these fractions were chromatographed on tlc with benzene and only one spot (R_f 0.55) was observed. The benzene was removed from these fractions *in vacuo*. The resulting solid was recrystallized ($EtOH-H_2O$) to yield 0.363 g (44.4%) of product: mp 186–187°; ir (KBr) 1725, 1700 (C=O), 1168 cm^{-1} (SO_2); nmr ($CDCl_3$) 0.91 (t, 6, J = 7 Hz, CH_3), 1.63 (m, 4, $-CH_2-$), 3.75 (t, 4, J = 7 Hz, CH_2N), and 7.85 ppm (s, 4, aromatic).

Anal. Calcd for $C_{15}H_{18}IN_3O_5S$: C, 37.59; H, 3.79; N, 8.77. Found: C, 37.75; H, 3.83; N, 8.83.

Thermal Degradation of 1-(*p*-Iodobenzenesulfonyl)-3,5-di-*n*-propyl Isocyanurate (1).—A solution of 0.2 g (0.0004 mol) of **1** in 9.8 ml of dimethylformamide and 0.2 ml of water was heated at 170° for 48 hr. The solvent was removed *in vacuo*, and the residual oil was dissolved in 10 ml of 1 *N* NaOH. The pH of the solution was adjusted to 6 with HCl and a solid precipitated. The product was recrystallized (H_2O) to yield 0.06 g (71%) of 1,3-di-*n*-propyl isocyanurate (**2**): mp 137–138° (lit.[8] mp 138°); ir (KBr) 3200 (NH), 1730, 1710 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) M^+ 213 (41).

Registry No.—**1**, 35105-49-8.

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(8) British Patent 928,637 (June 12, 1963); *Chem. Abstr.*, **60**, 2988 (1964).

The Synthesis and Reactions of a Tetrachlorodioxopiperazine

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For a projected synthesis, we required the amino acid derivative *N*-trifluoroacetyl-α-chlorosarcosyl chloride (**2**). When we applied the usual two-step procedure[2] for the synthesis of α-chloroacyl chlorides to *N*-trifluoroacetylsarcosine (**1**), using first thionyl then sulfuryl chloride, we isolated the α,α-disubstituted sarcosyl chloride **3** (~18% yield) in some reactions. The unexpected instability of **3**[3] and the identification of

$CH_3N(TFA)CXX'COX''$

1, X = X′ = H; X″ = OH
2, X = H; X′ = Cl; X″ = Cl
3, X = X′ = X″ = Cl

(TFA = F_3CCO-)

several of its decomposition products as fully chlorinated or ketalized diketopiperazines seemed of sufficient interest to warrant this interim report, especially so since *N*-trifluoroacetyl-α-chlorosarcosyl chloride (**2**), which we obtained recently, is stable and does not yield diketopiperazines on standing.

As expected the ir spectrum of **3** showed acid chloride (1775 cm^{-1}) and trifluoroacetylamide (1660 cm^{-1}) carbonyl absorptions (CCl_4), the nmr spectrum displayed the *N*-methyl signals only slightly shifted from **1**, but the signal for the α hydrogen was absent. Finally the electron-impact mass spectrum with the highest *m/e* peak at 236 corresponds to the molecular ion of **3** less one chlorine atom, behavior which might be expected for a geminal halide.

On standing in a stoppered flask at room temperature for 24 hr, however, the original colorless liquid changed largely to a crystalline mass (mp 128–130°) whose ir spectrum now showed only one absorption (1728 cm^{-1}) in the carbonyl region and a single *N*-methyl signal (singlet, δ 3.51) in the nmr spectrum. An electron-impact mass spectrum showed as the highest peak *m/e* 243; the true parent ion (*m/e* 278) could be detected with chemiionization techniques.[4] These data and the elemental analysis ($C_6H_6N_2O_2Cl_4$) suggested the sarcosine anhydride structure **6** for this product.

The route to **6** starts with loss of trifluoroacetyl chloride from **3** to give the imidoyl chloride **4**, which, being a reactive bifunctional species, could dimerize *via* **5** (Scheme I). The addition of acyl halides to imines has precedents.[5] To prove that the distillate (**3**) still had an intact *N*-trifluoroacetyl linkage, a sample was refluxed with octadecylamine (**10**) in benzene. *N*-Trifluoroacetyloctadecylamine (**11**) was isolated in 62% yield, identical in all respects with a sample prepared from **10** and trifluoroacetic anhydride. Low temperature trapping experiments designed to demonstrate the presence of trifluoroacetyl chloride in decomposing samples of **3** have so far been unsuccessful.

The diketopiperazine **6** possessed appreciable reactivity, as might be expected.[6] The addition of 1 equiv of triethylamine to a slurry of **6** in methanol initiated a rapid exothermic reaction to produce a 1:3 mixture of the soluble mono- and diketals **7** and **8**, which were separated by fractional crystallization. The mono-

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(2) E. Schwenk and D. Papa, *J. Amer. Chem. Soc.*, **70**, 3626 (1948).

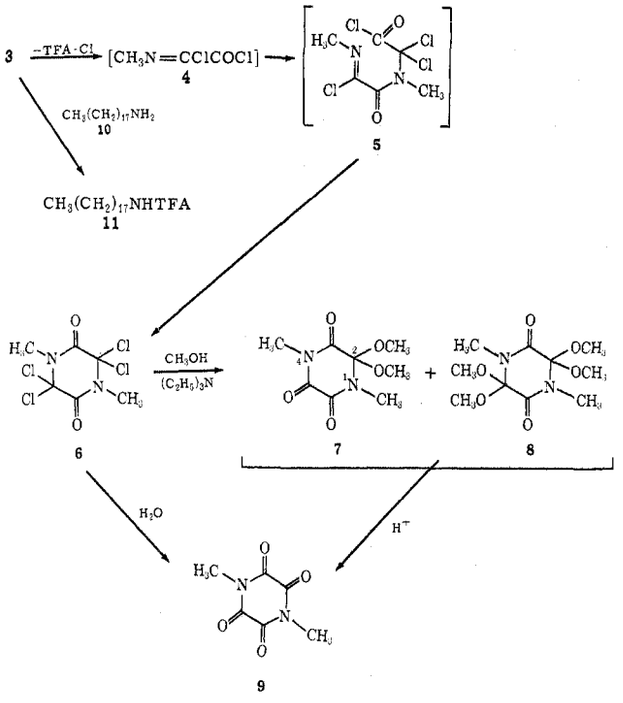
(3) F. Weygand and U. Glöckler, *Chem. Ber.*, **89**, 653 (1956).

(4) We thank Dr. Henry Fales, National Heart and Lung Institute, for this spectrum.

(5) A. H. Leuchs and A. Schlötzer, *Chem. Ber.*, **67**, 1572 (1934), and references cited therein.

(6) (a) P. W. Trown, *Biochem. Biophys. Res. Commun.*, **33**, 402 (1968); (b) H. Poisel and U. Schmidt, *Chem. Ber.*, **104**, 1714 (1971); (c) H. Böhme and K. Hartke, *ibid.*, **96**, 600 (1963).

SCHEME I



ketal **7**, mp 124–125°, exhibited nmr signals at δ 3.40, 3.34, and 3.05 in a 2:1:1 ratio (assigned to CH_3O, N_4 CH_3, and N_1 CH_3, respectively); the diketal **8**, mp 137–138°, had signals at δ 3.38 and 2.98 in a 2:1 ratio as expected for CH_3O and CH_3N protons. Surprisingly *both* **7** and **8** had only one amide carbonyl absorption in the ir region at 1702 and 1680 cm^{-1}, respectively. Finally, electron-impact mass spectrometry showed the parent molecular ions for **7** and **8** at *m/e* 216 and 262, respectively, as the highest peaks in the spectra.

When crystalline **6** was allowed to stand for 2 weeks in contact with the humid atmosphere, it decomposed to a material of the formula $C_6H_6N_2O_4$. A sample recrystallized from acetic acid had the characteristic melting point behavior of *N,N*-dimethyltetraketopiperazine **9**.[7] The ir spectrum (Nujol mull) showed one single carbonyl band (1695 cm^{-1}), the mass spectrum exhibited *m/e* 170 as the highest peak, and the nmr spectrum (trifluoroacetic acid) showed only one *N*-methyl singlet at δ 3.51. Exposure of the mixture of ketals **7** and **8** to acid also produced **9**. The tetrachlorodiketopiperazine **6** gave an immediate precipitate with silver nitrate and also a positive starch–iodide test.

Experimental Section

Ir spectra were measured with Perkin-Elmer spectrophotometers, Models 237B ($CHCl_3$ or CCl_4) and 421 (KBr). Mass spectra were obtained with the double-focusing Hitachi RMU-6E mass spectrometer. Pmr spectra were measured on the Varian Associates spectrometer, Model A-60. Chemical shifts are reported as δ values (parts per million) relative to tetramethylsilane as an internal standard; deuteriochloroform was used as solvent unless stated otherwise. Melting points were taken on a Koefler hot stage and are corrected. Thin layer chromatography (tlc) was carried out on 0.25-mm Merck precoated silica gel F-254 plates; spots were visualized with a hand uv lamp or iodine vapor.

N-Trifluoroacetylsarcosine (1).—The procedure of Weygand[8] was used. To a cooled solution (−10°) of 8.9 g (0.10 mol) of sarcosine in 60 ml of dry trifluoroacetic acid, 17.6 ml (0.12 mol) of trifluoroacetic anhydride was added over a period of 30 min. The mixture was stirred at −20° for 16 hr, then at room temperature for 1 hr, after which excess reagent and solvent were removed (bath temperature kept below 35°). The yellow residue was purified by vacuum distillation [bp 119–120° (1.1 mm)], yielding 11.0 g (0.59 mol, 59%) of a light yellow viscous oil which solidified upon cooling. This material was pure enough to be used in further experiments. A sample, crystallized from ethanol–hexane, had mp 54.5–55.5°. Tlc (acetic acid–benzene 7:1) showed one spot, R_f 0.25; ir (CCl_4) 1740 (amide), 1710 cm^{-1} (acid); nmr δ 10.7 (s, 1 H, COOH), 4.23 (s, 2 H, CH_2), 3.26 and 3.13 (4 lines, 1 line, respectively, 3 H, NCH_3, cis and trans isomers); mass spectrum (120°) *m/e* 185 (M^+), 141 ($M^+ - CO_2$), 140 ($M^+ - CO_2H$, base peak), 126, 112, 110, 97 (TFA), 90, 88 (M^+ − TFA), 78, 69, 60.

Anal. Calcd for $C_5H_6NO_3F_3$: C, 32.46; H, 3.27; N, 7.57. Found: C, 32.49; H, 3.50; N, 7.47.

N-Trifluoroacetyl-α,α-dichlorosarcosyl Chloride (3).—A solution of 19.0 g (0.103 mol) of **1** in 30 ml of freshly distilled thionyl chloride was refluxed for 2 hr. To the refluxing solution was then added 30 ml of freshly distilled sulfuryl chloride and refluxing was continued for another 2 hr. Excess reagents were removed by careful distillation and the light yellow residue was vacuum distilled, yielding 4.67 g (182 mmol, 18%) of a colorless liquid: bp 52–58° (16–18 mm); ir (CCl_4) 1865 (w), 1775 (s), 1660 cm^{-1} (m); mass spectrum (135°) *m/e* 236 (M^+ − Cl), 233, 174 ($M^+ - COCl_2$), 167 ($M^+ - Cl_3$), 140 ($M^+ - CF_3COCl$), 140 (CH_3N-CCl=C=O), 97 (TFA), 69 (CH_3NC=C=O).

2,2,5,5-Tetrachlorosarcosine Anhydride (6).—When 1.0 g of the above distillate was stored at room temperature in a stoppered flask for 24 hr, a crystalline mass formed, a sample of which on washing with dry hexane had mp 128–130°; ir (CCl_4) 1728 (s), 1420 (w), 1335 cm^{-1} (br m); nmr δ 3.51 (s); mass spectrum (200°), chemical ionization with 1 mm of methane, *m/e* 307 ($M^+ + C_2H_5$), 279 ($M^+ + 1$), 243 (M^+ − Cl), 216 (M^+ − COCl), 210, 209, 182, 181 ($M^+ - COCl_2$), 169, 168, 154, 147, 146, 141.

Anal. Calcd for $C_6H_6N_2O_2Cl_4$: C, 25.74; H, 2.16; N, 10.01. Found: C, 25.45; H, 2.19; N, 9.97.

N-Trifluoroacetyloctadecylamine (11).—To 4.0 g (15 mmol) of octadecylamine dissolved in the minimal amount of refluxing dry benzene was added 0.80 g (2.9 mmol) of distillate **3**. An exothermic reaction was observed. The clear solution was refluxed for 16 hr and cooled, and unreacted octadecylamine removed by filtration. The yellow filtrate was concentrated to dryness and then subjected to vacuum sublimation [105° (0.5 mm)] to yield 602 mg (1.8 mmol, 62%) of a colorless solid. Recrystallization from methanol gave needles: mp 73–74°; ir ($CHCl_3$) 3460 (sharp, NH), 2950, 2870, 1730 (CO), 1550, 1470 cm^{-1}; mass spectrum (160°) *m/e* 365 (M^+), 296 ($M^+ - CF_3$, base peak), 268 (M^+ − TFA), 97 (TFA), losses of *m/e* 14 and 28.

Authentic **11** was prepared as follows. To 4.0 g (15 mmol) of octadecylamine dissolved in the minimal amount of dry benzene was added, dropwise, 5 ml (excess) of trifluoroacetic anhydride. The solution was stirred at room temperature for 16 hr and for 1 hr at reflux. Solvent and excess reagent were removed and the colorless residue was recrystallized from methanol to yield 4.1 g (11.2 mmol, 75%) of a material that was identical in all respects with the amide described above.

2,2,5,5-Tetramethoxysarcosine Anhydride (8) and 2,2-Dimethoxy-5-ketosarcosine Anhydride (7).—To a stirred suspension of 40 mg of **6** in 3 ml of absolute methanol at room temperature was added 0.4 ml of triethylamine (hydrochloride vapors noted above the suspension). An exothermic reaction occurred resulting in a clear solution within 5 min. The solution was stirred at room temperature for 24 hr, and then the solvent was removed. The solid residue was extracted with ethyl acetate and water, the organic layer was dried (Na_2SO_4) and evaporated, and the residue was subjected to vacuum sublimation [90° (0.5 mm)] to yield 36 mg of a colorless solid which had the same nmr spectrum as the unsublimed material. The sublimate was recrystallized from chloroform–hexane which was allowed to evaporate slowly to yield 26 mg of large, cubic crystals (mp 137–138°) on the bottom and 8 mg of long, fine needles (mp 124–125°) on the wall of the flask.

(7) M. O. Forster and W. B. Saville, *J. Chem. Soc.*, **121**, 816 (1922).

(8) F. Weygand and R. Geiger, *Chem. Ber.*, **89**, 647 (1956).

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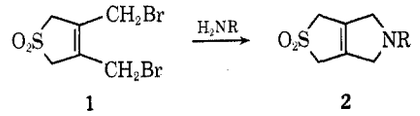
In a recent report,[3] it was indicated that, when 3,4-bis(bromomethyl)-2,5-dihydrothiophane 1,1-dioxide (**1**) was reacted with various amines even under



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).