ratories) for the 100-MHz NMR and field ionization mass spectral studies, respectively.

Registry No.—**1a,** 1793-07-3; **2a,** 55043-76-0; **2a** Schiff base, 55043-77-1; **2b,** 55043-78-2; **3,** 55043-79-3; **4,** 55043-80-6; **5b,** 4743-17-3; **6a,** 5100-23-2; **6b,** 18928-48-8; **7a,** 55043-81-7; **7b,** 55043-82-8; **8a,** 23829-79-0; **8b,** 23829-80-3; **10,** 1904-58-1; **12,** 30386-01-7; **13,** 55043-83-9; **18,** 7143-42-2; **19,** 85-91-6; **20,** 33923-02-3; **21,** 55043-84-0; **23,** 55043-85-1; **24,** 55043-86-2; **25,** 55043-87-3; methylhydrazine, 60-34-4; *p*-nitrobenzaldehyde, 555-16-8; potassium *tert*-butoxide, 3999-70-0; methanol, 67-56-1; urea, 57-13-6; ethyl chloroformate, 541-41-3.

References and Notes

(1) (a) G. A. Archer and L. H. Sternbach, *Chem. Rev.*, **68,** 747 (1968); (b) L. H. Sternbach in "The Benzodiazepines", Raven Press, New York, N.Y., 1973, pp 1–27.

(2) Class here refers to position of the nitrogen atoms in the triazepine ring and not to positions of unsaturation. The six classes, thus, refer to nitrogen atoms in the following positions: 1,3,4; 1,2,5; 1,3,5; 1,2,4; 1,2,3; and 2,3,4.

(3) For example, see H. Kohl, P. D. Desai, A. N. Dohadwalla, and N. J. de Souza, *J. Pharm. Sci.*, **63,** 838 (1974).

(4) (a) For example, see S. Rossi, British Patent 1,219,847; *Chem. Abstr.*, **74,** 141901j (1971); S. Rossi, German Patent 2,064,207; *Chem. Abstr.*, **75,** 76854a (1971). (b) We have developed a new entry into this class of compound in our laboratories which will be the subject of a later report.

(5) For example, see G. Doleschall, G. Hornyak, B. Agai, G. Simig, J. Fetter, and K. Lempert, *Tetrahedron Lett.*, 5069 (1973), and references cited therein.

(6) The structure of **2a** follows from spectral and chemical evidence. The NCH_3 and NH_2 signals in the NMR spectrum of **2a** appear as singlets at δ 3.19 and 3.97, respectively. Compound **2a** formed a Schiff base with *p*-nitrobenzaldehyde (see Experimental Section). Based on the known relative nucleophilicities of the nitrogen atoms in methylhydrazine, **2a** is the expected isomer from the reaction of **1a** with methylhydrazine. Other authors[7] have reported reactions of methylhydrazine with phenyl isocyanates to yield products analogous to **2,** but offer no evidence to distinguish their products from the other possible isomers.

(7) (a) M. Wilcox, *J. Med. Chem.*, **11,** 171 (1968); (b) French Patent 1,521,959; *Chem. Abstr.*, **71,** 3166k (1969).

(8) Y. Iwakura, K. Uno, and S. Kang, *J. Org. Chem.*, **31,** 142 (1966).

(9) O. Hromatka, F. Krenmüller, and M. Knollmüller, *Monatsh. Chem.*, **100,** 934 (1969).

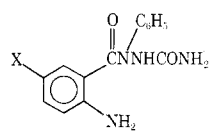
(10) (a) E. Thielepape, *Chem. Ber.*, **68,** 751 (1935); (b) W. S. Fones, *J. Org. Chem.*, **14,** 1099 (1949); (c) see also the preparation of **21** from **12** in the Experimental Section.

(11) A. K. Butler in "Organic Reaction Mechanisms", B. Capon and C. W. Rees, Ed., Wiley, New York, N.Y., 1972, p 189.

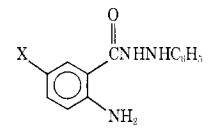
(12) A. L. Langis and M. P. Charest, *Chim. Ther.*, 349 (1967).

(13) R. L. Jacobs, *J. Heterocycl. Chem.*, **7,** 1337 (1970). We thank Dr. Jacobs, of Sherwin-Williams Chemicals, for an authentic sample of this compound. Compound **12** was also identical with a commercial sample of 3-amino-2,4(1*H*,3*H*)-quinazolinedione obtained from Carbolabs Inc., New Haven, Conn.

(14) Two of the benzotriazepinediones reported by Langis and Charest were prepared from the *N*-(2-aminobenzoyl)semicarbazides i and ii by thermal cyclization in decalin. Since the reported melting points for the products thus obtained from i and ii do not closely jibe, respectively, with those of compounds obtained from their treatment of iii and iv with urea in decalin (compounds which we suspect are quinazolinediones), the products derived from i and ii may be authentic benzotriazepinediones.



i, X = H
ii, X = Cl



iii, X = H
iv, X = Cl

(15) (a) D. M. Bailey, U.S. Patent 3,607,866 (1971); *Chem. Abstr.*, **75,** 140910v (1971); (b) Dr. Bailey has examined a preprint of this manuscript and concurs with these findings.

(16) N. P. Peet and S. Sunder, *J. Org. Chem.*, **39,** 1931 (1974).

(17) The structure of this material has been identified and will be disclosed in a future report.

(18) The reactant concentration in this preparation was 0.094 *M*. When run at a reactant concentration of 0.25 *M*, the yield of **7a** was 10.7%.

(19) E. Kühle and R. Wegler, *Justus Liebigs Ann. Chem.*, **616,** 183 (1958).

(20) An aliquot of the reaction mixture withdrawn at this point showed the precipitate to be **12.**

(21) G. B. Barlin, *J. Appl. Chem.*, **12,** 148 (1962).

(22) We have also prepared **10** by heating isotoic anhydride and hydrazine hydrate neat or in DMF at 50°.

(23) J. R. A. Pollack and R. Stevens, Ed., "Dictionary of Organic Compounds", Vol. . 4, Oxford University Press, London, 1965, p 2119.

(24) A. I. Vogel, "Practical Organic Chemistry", Longmans, Green and Co., New York, N.Y., 1956, p 1000.

Synthesis of Fused Phenothiazines. 2,3-Dihydro-1*H*-pyrimido[5,6,1-*kl*]phenothiazine-1,3-dione and 6*H*,16*H*-[1,5]Diazocino[3,2,1-*kl*:7,6,5-*k'l'*]diphenothiazine-6,16-dione

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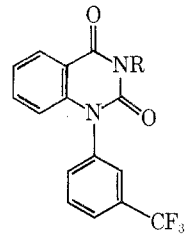
Smith Kline and French Laboratories, Philadelphia, Pennsylvania 19101

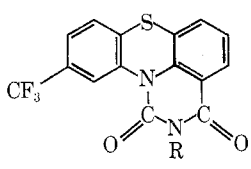
Received February 25, 1975

10-Trifluoromethyl-2,3-dihydro-1*H*-pyrimido[5,6,1-*kl*]phenothiazine-3-one-1-thione (**6**) was prepared starting from 8-trifluoromethylphenothiazine-1-carboxylic acid (**3**) by thermal cyclization of the acid isothiocyanate. This was converted to tee 1,3-dione by acid hydrolysis of the 1-methyl mercaptan derivative. Alkylation and oxidation to sulfoxide and sulfone derivatives are described. Pyrolysis of the anhydride of **3** gave 3,13-bis(trifluoromethyl)-6*H*,16*H*-[1,5]diazocino[3,2,1-*kl*:7,6,5-*k'l'*]diphenothiazine-6,16-dione.

Quinazoline-2,4-diones (**1**), derived from flufenamic acid, were recently described as anti-inflammatory agents.[1]



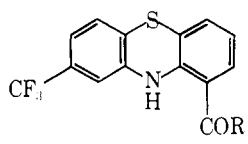
1



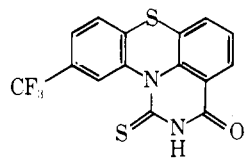
2

Since we previously observed anti-inflammatory properties with 8-trifluoromethylphenothiazine-1-carboxylic acid (**3**),[2] an analog of flufenamic acid, we undertook preparation of some pyrimidinediones (**2**) derived from **3.**

Typical syntheses of quinazolinediones such as **1** involve fusing the *N*-arylanthranilic acid, ester, or amide with urea, thiourea, or ethyl carbamate at 200°.[3] However, these reaction conditions using **3** returned unreacted starting material. Also treatment of the ethyl ester of **3** with sodium cyanate in trifluoroacetic acid, another quinazoline-1,3-dione synthesis,[4] also failed. A possible cause for these failures was a low reactivity of the diaryl nitrogen owing to it



3, R = OH
4, R = Cl
5, R = NCS



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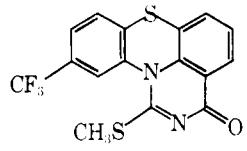

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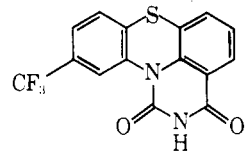

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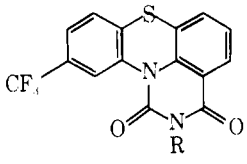
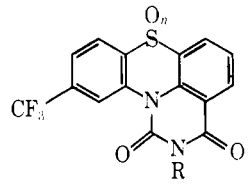


9, R = CH_2CH_3
10, R = CH_2CH_2OH
11, R = $CH_2CHOHCH_2OH$
12, R = $CH_2CHOAcCH_2OAc$



13, $n = 1$
14, $n = 2$

being part of the phenothiazine ring system. It appeared that building the new ring in a stepwise fashion using reactive intermediates might overcome this problem.

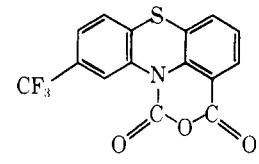
Reaction of **3** with phosphorus trichloride and dimethylformamide in chloroform gave the acid chloride **4** in 86% yield. Treatment of **4** with potassium thiocyanate in acetone gave **5** in 97% yield, which on heating to 220° in diphenyl ether cyclized to form **6** in 91% yield. Since attempts to hydrolyze **6** with chloroacetic acid failed, **6** was alkylated with iodomethane and potassium hydroxide in acetone to give **7** in 93% yield. Hydrolysis of this with HCl in aqueous ethanol gave the target compound **8** in 98% yield.

In order to obtain compounds likely to have the desired biological activity, **8** was alkylated using alkyl halides and sodium hydride in DMF to obtain **9** and **10**. Alkylation of **8** with 2,3-diacetoxy-1-chloropropane and subsequent hydrolysis with methanolic hydrochloric acid led to **11**. Oxidation of **8** and its N-alkylated derivatives with *m*-chloroperbenzoic acid gave the sulfoxides **13** shown in Table I. Oxidation with excess hydrogen peroxide in glacial acetic acid gave the sulfones **14** also shown in Table I.

Table I
2-Alkyl-10-trifluoromethyl-2,3-dihydro-1*H*-pyrimido[5,6,1-*kl*]phenothiazine-1,3-dione Sulfoxides (13) and Sulfones (14)[d]

Compd[a]	R	n	Yield, %	Mp, °C	S[c]
13a	H	1	76	302–304	M
14a	H	2	85	290–293	M
13b	CH_2CH_3	1	75	184–186	M
14b	CH_2CH_3	2	89	208–210	M
13c	CH_2CH_2OH	1	77	205–206	E
14c	CH_2CH_2OH	2	58	189–192	B
13d	$CH_2CHOHCH_2OH$	1	36	224–225	CM
14d	$CH_2CHOHCH_2OH$	2	90[b]	223–226	BM

[a] The compounds were characterized by ir (Nujol): sulfoxides ~9.5 μ and sulfones ~8.5 μ. [b] Crude yield. [c] Solvents of crystallization: B, 1-chlorobutane; C, chloroform; E, ethanol; M, methanol; CM, chloroform–methanol; BM, 1-chlorobutane–methanol. [d] Satisfactory analytical data (±0.3% for C, H, N) were reported for compounds **13a–d** and **14a–c**; the data for **14d** agreed with the formula $C_{18}H_{13}F_3N_2C_6S\cdot\frac{3}{4}H_2O$. Ed.



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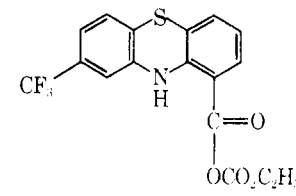

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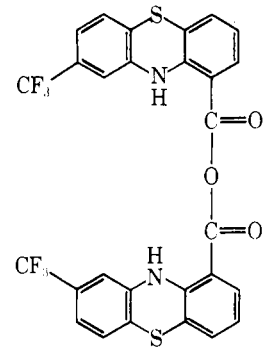
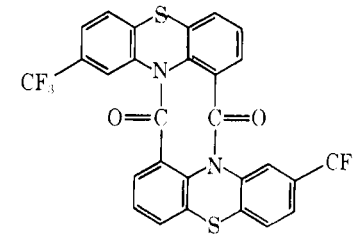
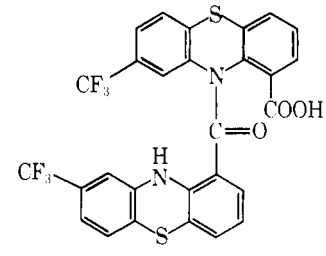


17



18



19

In an attempt to form the isatoic anhydride **15**, which is an oxygen analog of **2**, the triethylamine salt of the carboxylic acid **3** was treated with ethyl chloroformate.[5] This gave the mixed anhydride **16** in 81% yield. In an attempt to force the formation of **15**, **16** was heated at 260° for 20 min. However, the cyclic dilactam **18** was formed in about 30% yield. The structure of **18** was established by elemental analysis, absence of NH bonds in the ir, and correct M^+ ion in the mass spectrum. When the mixed anhydride was allowed to reflux with excess ethyl chloroformate, a red product was formed which was identified as the symmetrical anhydride **17**. Heating this in diphenyl ether gave **18** in 54% yield. In addition, **17** was seen in the reaction mixture during the pyrolysis of **16** to **18**, suggesting that it was an intermediate. An O to N acyl group migration in **17** could form **19**, which in turn could lose water to give **18**. Thus the conversion of **17** to **18** is facile because only intramolecular reactions are involved.

Experimental Section

Melting points (uncorrected) were determined using a Thomas-Hoover capillary melting point apparatus. NMR spectra were obtained in a Varian T-60 instrument, and ir on a Perkin-Elmer 735 infrared spectrophotometer. Mass spectra were determined using a Hitachi Perkin-Elmer RMN-6E spectrometer. For thin layer chromatography the following solvent systems were used: chloroform for **4** and **5**; 75% chloroform–cyclohexane for **16**, **17**, and **18**; and 95% chloroform–methanol for all the other compounds.

8-Trifluoromethylphenothiazine-1-carboxylic Acid Chloride (4). 8-Trifluoromethylphenothiazine-1-carboxylic acid (62.2 g, 0.20 mol) was added to a stirred mixture of chloroform (300 ml) and phosphorus trichloride (300 ml). The resulting brown suspension was cooled in an ice bath while dimethylformamide (50 ml) was added slowly until a reddish brown solution formed. After the mixture was stirred for 4 hr at room temperature, the chloroform and excess phosphorus trichloride were evaporated under reduced pressure. The resulting reddish-brown solid residue was dissolved in boiling *n*-hexane (1.5 l.). The hot clear reddish solution was decanted from a viscous, insoluble material, and on cooling, large red

needles formed. The solid was collected by filtration and washed with hexane to give 57.0 g (86%) of the desired product: mp 124–126°; ir (Nujol) 3.00 (NH), 5.86 μ (C=O).

8-Trifluoromethylphenothiazine-1-carboxylic Acid Isothiocyanate (5). A solution of 56.5 g (0.172 mol) of 8-trifluoromethylphenothiazine-1-carboxylic acid chloride in 450 ml of acetone was added over a 15-min period to a stirred solution of 25.0 g (0.257 mol) of potassium thiocyanate in 200 ml of acetone. The resulting reddish-brown suspension was stirred at room temperature for 1.5 hr. The reaction mixture was concentrated under reduced pressure to approximately 300 ml and then diluted with 700 ml of water. The product was collected by filtration and washed thoroughly with water to give 58.7 g (97%) of light brown crystals: mp 145–150°; ir (Nujol) 5.10 (N=C=S), 5.86 μ (C=O); NMR ($CDCl_3$) δ 6.55–7.39 (m, 5 H, 3,4,6,7,9-H), 7.60 (d, 1 H, 2-H), 10.6 (s, 1 H, NH).

10-Trifluoromethyl-2,3-dihydro-1*H*-pyrimido[5,6,1-*kl*]phenothiazin-3-one-1-thione (6). A slurry of 53.7 g (0.168 mol) of **5** in 30 ml of diphenyl ether was heated in an oil bath at 210° for 1 hr. The reaction mixture first became a homogenous liquid and then turned into a solid mass. The cooled reaction mixture was refluxed for several minutes in 100 ml of toluene and cooled to room temperature, and the insoluble material was collected by filtration and washed with several small portions of toluene to give 48.7 g (91%) of a yellowish product, mp 296–299°. The material was sufficiently pure for use in the next step. A small sample was recrystallized from ethanol for analysis: mp 297–299°; ir (Nujol) 3.12 and 3.22 (NH), 5.85 μ (C=O); NMR ($CDCl_3$–DMSO-d_6) δ 7.20–8.15 (m, 5 H, 4,5,6,8,9-H), 8.49 (s, 1 H, 11-H), 13.00 (s, 1 H, NH).

1-Methylmercapto-10-trifluoromethyl-3*H*-pyrimido[5,6,1-*kl*]phenothiazin-3-one (7). A 53.6-g (0.152 mol) sample of **6** was added to a stirred solution of 8.95 g (0.160 mol) of potassium hydroxide in 1680 ml of acetone and 720 ml of water. After all the solid had dissolved and a clear yellow solution formed, 22.8 g (10 ml, 0.160 mol) of methyl iodide was added all at once. A slight rise in temperature was noticed, and 2 min later the product began to precipitate. The reaction mixture was stirred at room temperature for 18 hr, diluted with 1 l. of water, and then chilled in an ice bath for several hours. The resulting light yellow solid was collected by filtration and washed with water to give 51.5 g (93%) of product, mp 225–228°. The material was used in the next step without any further purification. A small sample was crystallized from ethanol for analysis: mp 229–231°; ir (Nujol) 5.91 μ (C=O); NMR ($CDCl_3$ δ 2.75 (s, 3 H, CH_3S), 7.44 (m, 4 H), 8.00 (m, 2 H).

10-Trifluoromethyl-2,3-dihydro-1*H*-pyrimido[5,6,1-*kl*]phenothiazine-1,3-dione (8). A stirred suspension of 53.6 g (0.146 mol) of **7** in 240 ml of concentrated hydrochloric acid and 800 ml of ethanol was heated under reflux for 4 hr. After the reaction mixture was concentrated to approximately one-half its original volume by boiling off the excess solvents, and then chilled, the product was collected by filtration and washed thoroughly with water to give 47.7 g (98%) of pale yellow needles, mp 278–280°. A sample was crystallized from ethanol: mp 278–280°; ir (Nujol) 3.12 and 3.3 (NH), 5.80 and 5.89 μ (C=O); NMR ($CDCl_3$–DMSO-d_6) δ 7.60–8.00 (m, 5 H), 8.10 (s, 1 H, 11-H), 11.80 (s, 1 H, NH).

Alkylation of the Pyrimidophenothiazine-1,3-dione (8). Preparation of 2-Ethyl-10-trifluoromethyl-2,3-dihydro-1*H*-pyrimido[5,6,1-*kl*]phenothiazine-1,3-dione (9). A 4.2-g (0.100 mol) sample of 57% sodium hydride in mineral oil was added to a stirred solution of 28.0 g (0.0834 mol) of **8** in 220 ml of dry dimethylformamide. The mixture was stirred for 1 hr at room temperature, then 16.8 g (8.6 ml, 0.108 mol) of ethyl iodide was added. The resulting greenish-yellow turbid mixture was stirred for 4.5 hr at room temperature and then filtered to give a clear yellow solution. The filtrate was evaporated to dryness under reduced pressure, and the pasty residue was triturated with petroleum ether to remove the mineral oil. The crude solid product was precipitated from a methanol–water mixture to give 28.8 g of a yellow powder. The material was crystallized from ethanol to give 23.2 g (73%), mp 148–150°. A further crystallization of a small sample raised the melting point to 150–152°: ir (Nujol) 5.82 and 5.95 μ (C=O); NMR ($CDCl_3$) δ 1.40 (t, 3 H, CH_3) 4.21 (q, 2 H, CH_2), 7.10–7.70 (m, 6 H) 7.85–8.2 (m, 2 H).

A twofold excess of sodium hydride and a fourfold excess of 2-bromoethanol were used to prepare **10.** The crude material was purified by column chromatography (silica gel, chloroform, and then 90% chloroform–methanol). The product crystallized from methanol in 47% yield: mp 90–93°; ir (Nujol) 2.95 (broad OH), 5.82 and 6.00 μ (C=O); NMR ($CDCl_3$) δ 2.75 (s, broad, 1 H, OH), 3.92 and 4.40 (2 t, 4 H, CH_2CH_2), 7.00–7.80 (m, 5 H), 7.90 (s, 1 H, 11-H).

3-Chloro-1,2-diacetoxypropane,[6] bp 80–83° (0.1 mm) (0.112 mol), and sodium hydride (0.0801 mol) were used to prepare **12.** The reaction mixture was heated at 100–110° for 40 hr in the presence of a catalytic amount of potassium iodide. The product was isolated as an oil and was used in the next step without purification. A small amount was purified by column chromatography (silica gel, chloroform) for spectral studies: ir (neat) 5.70 (C=O, acetyl), 5.80 and 5.95 μ (C=O, dione); NMR ($CDCl_3$) δ 2.08 and 2.12 (2 s, 6 H, 2 CH_3), 3.6–4.8 (m, 5 H, CH_2CHCH_2), 7.40 (m, 4 H), 8.00 (m, 2 H).

2-(2,3-Dihydroxypropyl)-10-trifluoromethyl-2,3-dihydro-1*H*-pyrimido[5,6,1-*kl*]phenothiazine-1,3-dione (11). A mixture of 48.1 g (0.0975 mol) of the crude **12** in 200 ml of methanol and 25 ml of concentrated hydrochloric acid was heated under reflux for 0.5 hr, then allowed to stand overnight at room temperature. The white solid that precipitated was isolated by filtration and washed with water to give 12.9 g of crude **11.** Additional material was obtained from the mother liquor. Overall crude yield was 24.6 g (62%). The first crop was recrystallized twice from chloroform to give 10.13 g of product: mp 159–162°; ir 2.96–3.06 (broad OH), 5.82 and 5.95 μ (C=O); NMR ($CDCl_3$–DMSO-d_6) δ 3.60 and 3.66 (2 s, 2 H, 2 OH), 3.8–4.68 (m, 5 H, CH_2CHCH_2), 7.00–7.60 (m, 4 H), 7.70–8.10 (m, 2 H).

Oxidation of the Pyrimidophenothiazine-1,3-diones. Preparation of the Sulfoxides. A 10% excess of *m*-chloroperbenzoic acid was added in small portions to a stirred, cold (0–5°) solution or suspension of the substrate (1 g/10 ml) in absolute methanol. The resulting mixture was stirred for 0.5–1 hr in the cold and then for an additional 1–4 hr at room temperature. The product precipitated from the reaction mixture, and after chilling was collected by filtration and washed with ice-cold methanol.

Preparation of the Sulfones. A solution of the substrate in glacial acetic acid (1 g/20 ml) and 3 equiv of 30% hydrogen perioxide was heated at 75–85° for 3–6 hr, cooled, and diluted with water to precipitate the product. The product was collected by filtration and washed with water.

Carbonic Acid Monoanhydride with 8-Trifluoromethylphenothiazine-1-carboxylic Acid Ethyl Ester (16). Triethylamine (3.04 ml, 0.022 mol) was added dropwise to a cold (0–5°), stirred suspension of 8-trifluoromethylphenothiazine-1-carboxylic acid (6.22 g, 0.020 mol) in 40 ml of ethyl chloroformate. The resulting orange suspension was stirred at room temperature for 15 hr, then diluted with dry benzene (100 ml), and the insoluble triethylamine hydrochloride was removed by filtration. After the filtrate was evaporated under reduced pressure, the solid, orange residue was suspended in light petroleum ether (50 ml) and filtered to give 6.22 g (81%) of the mixed anhydride: mp 91–94°; ir (Nujol) 3.02 (NH), 5.55 and 5.85 μ (C=O); NMR ($CDCl_3$) δ 1.40 (t, 3 H, CH_3), 4.40 (q, 2 H, CH_2), 6.60–7.29 (m, 5 H), 7.50 and 7.60 (2 d, 1 H, 2-H), 9.81 (s, 1 H, NH).

8-Trifluoromethylphenothiazine-1-carboxylic Acid Anhydride (17). A solution of 3.0 g (0.00785 mol) of **16** in 10 ml of ethyl chloroformate was heated under reflux for 18 hr. The dark red solution was chilled in an ice bath, and the resulting orange precipitate was collected by filtration and washed with a small portion of ethyl chloroformate and then with light petroleum ether to give 0.87 g (50%) of product, mp 207–208°. The mother liquor was evaporated under reduced pressure, and the oily residue was found to be unreacted starting material. A small sample of **17** was crystallized from chloroform for analysis: mp 207–209°; ir (Nujol) 3.2 (NH), 5.71 and 6.90 μ (C=O); NMR ($CDCl_3$) δ 6.60–7.20 (m, 10 H, 3,4,5,6,7,9- and 3′,4′,5′,6′,7′,9′-H), 7.55 and 7.69 (2 d, 2 H, 2- and 2′-H), 9.80 (s, 2 H, 2 NH).

3,13-Bis(trifluoromethyl)-6*H*,16*H*-[1,5]diazocine[3,2,1-*kl*:7,6,5-*k′l′*]diphenothiazine-6,16-dione (18). A mixture of 1.50 g (0.00239 mol) of **17** and 2 ml of diphenyl ether was heated in an oil bath at 260–265° for 45 min, producing a dark, olive-green solution which solidified when cooled to room temperature. Light petroleum ether (30 ml) was added to the cooled reaction mixture, and the insoluble material was collected by filtration and washed with a small portion of petroleum ether to give 1.22 g of yellow powder. This was dissolved in 50 ml of chloroform, and the resulting solution was extracted with 5% sodium bicarbonate to remove some acid **3.** The chloroform layer was dried with anhydrous sodium sulfate and the resulting dark amber solution was decolorized with Norit. The resulting yellow solution was concentrated to approximately 15 ml and diluted with 50 ml of petroleum ether. After the mixture was chilled in an ice bath for several hours, the light yellow, crystalline product was collected by filtration and washed with petroleum ether to give 0.75 g (54%) of **18:** mp 295–297°; ir

6.90 μ (C=O); NMR (TFA) δ 7.20–7.80 (m, 10 H, 1,2,7,8,9,11,12,17,18,19-H), 8.10 (s, 2 H, 4,14-H); mass spectrum *m/e* 586 (M^+).

Compound 18 was also prepared by pyrolyzing 17 at 260°; the yields, however, were lower.

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References and Notes

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New Syntheses of Thiadiazinones, Thiazolidinedione Hydrazones, and Hydroxythiazoles from Phenyl(trichloromethyl)carbinols[1]

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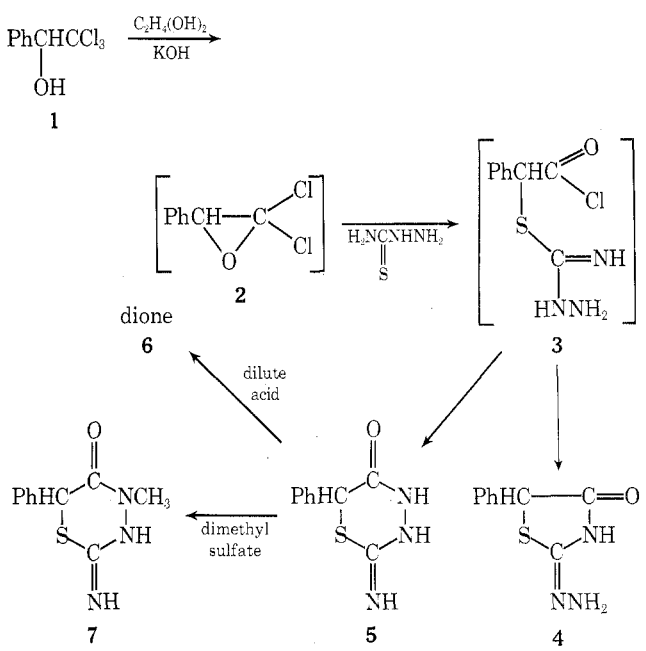
Phenyl(trichloromethyl)carbinol reacts with thiosemicarbazide under basic reaction conditions to form dihydro-2-imino-6-phenyl-2*H*-1,3,4-thiadiazin-5(6*H*)-one (**5,** 18% yield) and 5-phenyl-2,4-thiazolidinedione 2-hydrazone (**4,** 10% yield), with acetone or benzaldehyde thiosemicarbazones to form derivatives of **4** (65% yield), and with thioacetamide to form 4-hydroxy-2-methyl-5-phenylthiazole (**11,** 18% yield). In the first step of the synthesis of these compounds, phenyl(trichloromethyl)carbinol is postulated to be converted into a dichloro epoxide **2,** and this is attacked by the thioenolate anion of the nucleophile to form an amino acid chloride which then undergoes ring closure to form the heterocyclic ring. The chemistry of the various compounds is discussed.

We have reported two reactions of phenyl(trichloromethyl)carbinol (1) with nucleophiles resulting in the formation of heterocyclic rings.[2,3] The thiourea case[2] provides an excellent example of a nucleophile with two reactive sites reacting initially at the α carbon of the carbinol followed by a subsequent ring closure to form the heterocyclic ring. The purpose of this research was to extend the thiourea work to other nucleophiles likewise having two reactive sites. The mechanisms by which methoxide reacts with phenyl(trichloromethyl)carbinol to form α-methoxyphenylacetic acid have been elucidated,[4] and by analogy, the nucleophiles studied here are believed to react by the mechanism given below in Scheme I.

Thiosemicarbazide. The first nucleophile examined was thiosemicarbazide. The initial step in the reaction of this with phenyl(trichloromethyl)carbinol dissolved in ethylene glycol containing potassium hydroxide involves the attack of the thioenolate anion at the α carbon of the intermediate epoxide (**2**) formed in situ from the carbinol (**1**). The postulated intermediate **3** has three –NH– groups available for reaction with the acid chloride and two (**4** and **5**) of the three possible compounds were formed. Compound **5,** dihydro-2-imino-6-phenyl-2*H*-1,3,4-thiadiazin-5(6*H*)-one, was easily isolated (as the monohydrate) in 18% yield because of its insolubility in the reaction mixture in the pH range of 9.4–5. The structure of this new compound was proven as follows. Hydrolysis with dilute acid gives ammonia and dione **6;** elemental analysis of **6** shows that it must contain the hydrazine moiety so that the ring closure must occur by the acid chloride (**3**) reacting with the hydrazine function. Compound **6** is neutral as would be expected for a diamide; this rules out the 3-amino-2-imino-5-phenyl-4-thiazolidinone structure and establishes the presence of the thiadiazinone ring. This was further collaborated by

Scheme I



methylation of **5** with dimethyl sulfate and alkali; only a monomethyl derivative (**7**) could be isolated whereas the aminothiazolidinone should form a dimethyl derivative. As expected, **7** could be hydrolyzed to a neutral dione with 2 *N* hydrochloric acid. The position of the methyl group in **7** was established by desulfurization with Raney nickel to *N*-methylphenylacetamide. Upon refluxing **7** with 20% hydrochloric acid for 3 hr the diazine ring opened and reclosed to form 5-phenyl-2,4-thiazolidinedione in 85% yield