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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Registry No.—**3,** 7220-56-6; **4,** 24539-01-3; **5,** 55223-38-6; **6,** 55223-39-7; **7,** 55223-40-0; **8,** 55223-41-1; **9,** 55223-42-2; **10,** 55223-43-3; **11,** 55223-44-4; **12,** 55223-45-5; **13a,** 55223-46-6; **13b,** 55223-47-7; **13c,** 55223-48-8; **13d,** 55223-49-9; **14a,** 55223-50-2; **14b,** 55223-51-3; **14c,** 55223-52-4; **14d,** 55223-53-5; **16,** 55637-96-2; **17,** 55223-54-6; **18,** 55223-55-7; 3-chloro-1,2-diacetoxypropane, 869-50-1.

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

Wilkins Reeve* and Eugene R. Barron

Chemistry Department, University of Maryland, College Park, Maryland 20742

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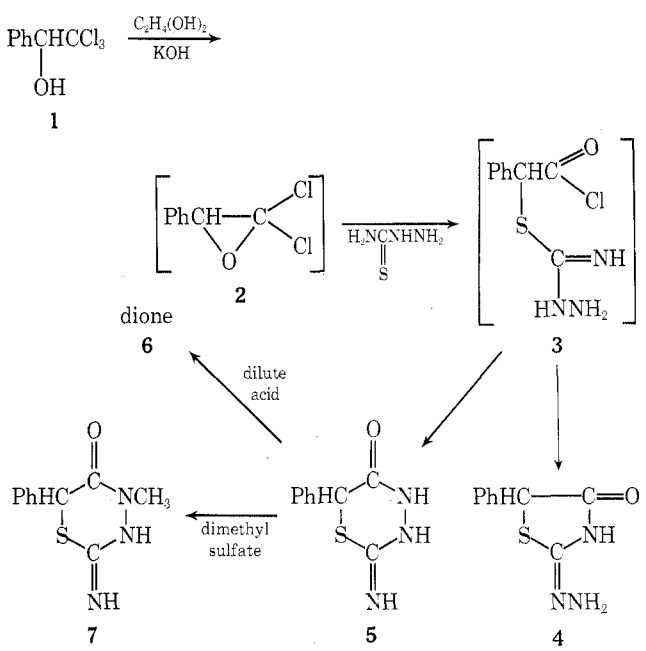
Phenyl(trichloromethyl)carbinol reacts with thiosemicarbazide under basic reaction conditions to form dihydro-2-imino-6-phenyl-2*H*-1,3,4-thiadiazin-5(6*H*)-one (**5,** 18% yield) and 5-phenyl-2,4-thiazolidinedione 2-hydrazone (**4,** 10% yield), with acetone or benzaldehyde thiosemicarbazones to form 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

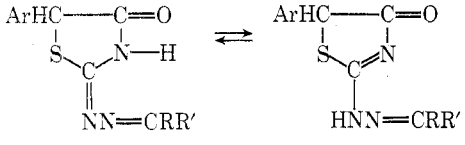


methylation of **5** with dimethyl sulfate and alkali; only a monomethyl derivative (**7**) could be isolated whereas the aminothiazolidinone should form a dimethyl derivative. As expected, **7** could be hydrolyzed to a neutral dione with 2 *N* hydrochloric acid. The position of the methyl group in **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

together with methylhydrazine, isolated as the sulfate. This rearrangment of 1,3,4-thiadiazines to five-membered rings in strongly acid solution is frequently observed.[5] Under the same hydrolysis conditions, hydrazine was obtained from **5.**

After **5** was filtered off, compound **4** remained in solution and was too soluble to be isolated directly. On adding acetone, the known 5-phenyl-2,4-thiazolidinedione-2-isopropylidenehydrazone slowly precipitated (10% yield) over a period of 1 week. After removal of **4,** acidification of the reaction mixture gave a crude acid fraction which was converted to a mixture of methyl esters. Sixteen components were shown to be present by GLC. Of these the major peak (63% of the ester mixture, 8% yield) was methyl phenylacetate, identified by comparison of the ir and NMR spectra of a collected sample with those of an authentic sample.

Thiosemicarbazones. The thiosemicarbazones of acetone and benzaldehyde were found to react with phenyl(trichloromethyl)carbinol under the same reaction conditions to give the known thiazolidinones **8a** and **8b.** The six-membered ring thiadiazinones cannot be formed from the semicarbazones, and the thiazolidinones are therefore obtained in higher yields.



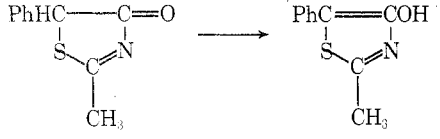
8 **9**

a, Ar = Ph; R = CH_3; R′ = CH_3; 63% yield
b, Ar = Ph; R = Ph; R′ = H; 69% yield
c, Ar = *p*-ClPh; R = CH_3; R′ = CH_3; 79% yield
d, Ar = *p*-CH_3OPh; R = CH_3; R′ = CH_3; 31% yield

The mechanism of formation of these compounds is the same as that shown for compound **4** (Scheme I). Tautomeric structures such as **9** can be written for the **8** series of compounds but NMR spectral evidence supports formula **8.** All of the series **8** compounds have very similar chemical shifts for the carbon-5 proton (δ 5.5), and for the NH proton (δ 12). This latter value is reasonable for structure **8** since the corresponding imino proton of 5-phenyl-2,4-thiazolidinedione has a δ 12.2 value. The alternate structure **9** would be expected to have the NH resonance occur around δ 10.3, the value for the NH proton of benzaldehyde phenylhydrazone.

The reactions of *p*-chlorophenyl(trichloromethyl)carbinol and *p*-methoxyphenyl(trichloromethyl)carbinol with acetone thiosemicarbazone were also studied to see if the yields of products obtained followed the same trends previously observed in the reactions of these carbinols with cyanamide[3] or methoxide;[6] this was found to be the case. The effect of the negative groups was to raise the yield whereas the presence of the *p*-methoxy substituent caused the yield to be halved.

Thioamides. A third class of nucleophiles with the S=CNH– function are the thioamides. Thioacetamide was allowed to react with phenyl(trichloromethyl)carbinol under the same conditions as before, and 4-hydroxy-2-methyl-5-phenylthiazole (**11**) was isolated in 18% yield.



10 **11**

The formation of the hydroxythiazole involves the attack of the thioenolate anion on the epoxide **2** in a manner strictly analogous to that given in Scheme I, followed by ring closure to **10** and enolization to **11.** The structure of this new compound was established from its chemical reactions and its spectral data. Hydrolysis with strong base gave α-mercaptophenylacetic acid, isolated as dithiobis(phenylacetic acid). A molecular weight determined by the Rast method demonstrated **11** to be monomeric. The material forms an acetate derivative with acetic anhydride. That the hydroxythiazole and its acetate exist entirely in the enol form follows from their ir and NMR spectra. The hydroxythiazole exhibits a broad absorption band at 2700–2000 cm^{-1}, suggestive of a hydrogen-bonded hydroxyl group, and there is no carbonyl absorption in the expected 1650–1800-cm^{-1} range. Its NMR spectrum shows a broad singlet at δ 11.2 characteristic of an enol. Structure **10** would have a characteristic carbon-5 proton resonance at δ 5.7 and this is missing from both the hydroxythiazole and its acetate ester. The above spectral data conclusively show the product to be in the enol form **11** rather than the keto form **10.** This is quite interesting, since 4-hydroxythiazoles, like hydroxythiophenes, usually exist mostly in the keto form and are labile substances which decompose in a few days even at room temperature.[7] In contrast, a sample of **11** has not undergone any decomposition, as judged by its ir spectra, after standing for 7 years at room temperature protected from light. Jensen's 4-hydroxythiazoles had a phenyl group substituted at the 2 position[7] and it would appear that the presence of the phenyl group in our compound at the 5 position, in conjugation with the double bond, stabilizes the enolic form.

Unlike Jensen's 4-hydroxy-2-phenylthiazoles,[7] compound **11** remains in the monomeric form on refluxing a solution of it dissolved in either water, benzene, or alcohol. It was soluble in dilute base and reprecipitated unchanged on acidification. However, exposure to sunlight for several months changed approximately half of the sample to a dark tan, insoluble, polymeric material, which, however, slowly dissolved in sodium hydroxide solution and then yielded **11** on acidification. The polymeric material analyzed for $C_{10}H_9NOS$, like **11,** but had a strong carbonyl absorption at 1695 cm^{-1} and no absorption around 2500 cm^{-1}. It is obviously some polymeric form of **10,** but its exact structure is unknown.

After removal of the hydroxythiazole, a large crude acid fraction was isolated which accounted for all of the remaining phenyl(trichloromethyl)carbinol. Esterification with methanol, followed by GLC analysis of the ester mixture, showed it to be a mixture of ten compounds of which the major one (58%) was methyl phenylacetate.

Thiocyanate. Another nucleophile with both sulfur and nitrogen bonded to a carbon is thiocyanate anion. Unfortunately, a complex mixture of products resulted from the reaction of this nucleophile with phenyl(trichloromethyl)carbinol, and only dithiobis(phenylacetic acid) and thiobis(phenylacetic acid) could be isolated in 17 and 3% yields, respectively. Again there was a large crude acid fraction. This was converted into a mixture of methyl esters with diazomethane and shown to consist of 16 components by GLC. The major compound (36%) was methyl phenylacetate.

Comments on Nucleophiles. Thiourea and the three classes of nucleophiles studied here all have the –NHC=S moiety in common and all react satisfactorily with phenyl(trichloromethyl)carbinols. The sulfur anions of these compounds are highly reactive in the SN2 epoxide ring opening reaction; they are so much more reactive than the anion from the solvent, ethylene glycol, that the solvent does not compete. The high reactivity of the amino group toward

the acid chloride causes the heterocyclic ring to form. The initial attack on the epoxide ring by the sulfur anion is the most important of the various steps involved. Evidence for this comes from our unsuccessful attempts to substitute urea for thiourea. Despite repeated attempts under varying conditions, none of the substituted oxazolidinone could be obtained. Guanidine was another nucleophile which failed to react with phenyl(trichloromethyl)carbinol under the usual conditions, presumably because all of the guanidine was in the form of the unreactive guanidinium ion.

Experimental Section

All melting points and boiling points are corrected. The ir spectra were recorded on a Perkin-Elmer Model 337. The NMR spectra were recorded on a Varian Model A-60 with tetramethylsilane as the internal standard. When dimethyl sulfoxide was used a solvent, the solvent peak at δ 2.62 was used as the reference. Analyses are by Dr. Franz J. Kasler.

Dihydro-2-imino-6-phenyl-2*H*-1,3,4-thiadiazin-5(6*H*)-one (5). To a solution of 68 g (0.3 mol) of phenyl(trichloromethyl)carbinol[8] and 45.5 g (0.5 mol) of thiosemicarbazide in 500 ml of ethylene glycol was added dropwise, over a 75-min period, a solution of 110 g (1.7 mol) of potassium hydroxide pellets in 350 ml of ethylene glycol. The temperature was maintained at 46–47° during the addition and kept at this temperature for an additional 2 hr. As the reaction proceeded the color of the reaction mixture became deep brown. The insoluble potassium chloride was filtered off and washed with methanol. The mother liquor was diluted with an equal volume of ice and water, and extracted twice with a large volume of ether. The chilled aqueous solution was acidified to pH 9.4 with hydrochloric acid; a heavy precipitate formed immediately. The mixture was chilled overnight and filtered, and the crude product (11.7 g, 18% of theory) was washed thoroughly with water. When inserted in the melting point bath at 177° the material decomposed at 187–188°. The infrared spectrum of this crude material was identical with that of a pure sample. The product was purified by dissolving in 250 ml of 95% ethanol, decolorizing, filtering, and diluting with 100 ml of water. There was obtained 10.6 g of dihydro-2-imino-6-phenyl-2*H*-1,3,4-thiadiazin-5-(6*H*)-one monohydrate. An analytical sample was prepared by recrystallizing the material two additional times from water–ethanol: mp 188.5–189.5° dec; ir (KBr) 3425, 3310, 3180, 3030, 2915, 1625, 1580, 1470, 1400, 1340, and 730 cm^{-1}; NMR (DMSO) δ 10.42 [s, 1, –C(=NH)NHN**H**–], 7.38 (s, 5, Ph), 6.15 [s, 2, –C(=N**H**)N**H**NH–], 4.83 (s, 1, >CH–), 3.72 (s, 2, H_2O).

Anal. Calcd for $C_9H_{11}N_3O_2S$: C, 47.99; H, 4.92; N, 18.65; S, 14.23. Found: C, 48.07; H, 5.16; N, 18.40; S, 14.18.

The anhydrous material was prepared by heating the monohydrate in a vacuum oven at 70° for 4 hr. A 1.0527-g sample of the monohydrate lost 0.0826 g of water or 7.85% of its weight (theory, 8.00%): mp 189–190°; ir (KBr) 3440, 3280, 3150, 2910, 1640, 1590, 1470, 1375, 1325, 1250, 1030, 865, 740, 695, and 530 cm^{-1}; NMR (DMSO) δ 10.57 [s, 1, –C=NH)NHN**H**–], 7.43 (s, 5, Ph), 6.21 [s, 2, –C(=N**H**)N**H**NH–], 4.92 (s, 1, >CH–).

Anal. Calcd for $C_9H_9N_3OS$: C, 52.16; H, 4.38. Found: C, 52.04; H, 4.60.

Dihydro-6-phenyl-2*H*-1,3,4-thiadiazine-2,5(6*H*)-dione (6). The above material (**5** monohydrate) was hydrolyzed to **6** by refluxing 4 g with 78 ml of 28% sulfuric acid for 40 min. Water (75 ml) was added and the mixture was chilled in an ice bath. White crystals and some gum-like material separated from the solution. The gum was discarded and the crystalline material filtered and washed with cyclohexane, giving 1.8 g of material (51% of theory). Crystallization from 60 ml of 95% ethanol gave 0.85 g of the almost pure **6**, mp 130–132°. After two additional recrystallizations the melting point was 135°; ir (KBr) 3350, 3270, 3200, 1760, 1690, 1600, 1490, 1460, 1390, 1175, 920 855, 775, 740, 705, 640, and 535 cm^{-1}; NMR (DMSO) δ 7.6 (s, 5, Ph), 5.86 (s, 1, >CH), 5.3 (broad s, 2, –NH–).

Anal. Calcd for $C_9H_8N_2O_2S$: C, 51.91; H, 3.87; N, 13.45; S, 15.40. Found: C, 52.06; H, 4.10; N, 13.41; S, 15.60.

The dione **6** can also be prepared by substituting 2 *N* hydrochloric acid for the 20% sulfuric acid; however, if 20% hydrochloric acid is used, 5-phenyl-2,4-thiazolidinedione is formed.

Dihydro-2-imino-4-methyl-6-phenyl-2*H*-1,3,4-thiadiazin-5(6*H*)-one (7). Compound **5** (4.85 g, 0.0215 mol of the monohydrate) was suspended in 100 ml of 2 *N* sodium hydroxide and 18 ml of dimethyl sulfate was added over a period of 1 hr while the flask was maintained at room temperature. The reaction mixture was stirred for an additional 1 hr and chilled in an ice bath, and the precipitate (3.5 g, 74% of theory) was filtered and washed, first with water and then with cyclohexane. The melting point was 167.5–169.5°; this was raised to 171° by recrystallization first from a water–alcohol mixture and then from 95% alcohol. Ir (KBr) 3400, 3320, 3185, 2930, 1620, 1550, 1450, 1390, 1340, 1230, 1090, 980, 835, 775, 745, 725, 690, and 530 cm^{-1}; NMR (DMSO) δ 7.53, (s, 5, Ph), 6.50 (s, 2, =NH and –NH–), 5.06 (s, 1, >CH–), 3.03 (s, $-CH_3$).

Anal. Calcd for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99; S, 14.49. Found: C, 54.34; H, 5.14; N, 19.10; S, 14.49.

The methyl group of **7** was proven to be in the 4 position by refluxing 1.3 g of **7** dissolved in 80 ml of ethanol with 30 g of Raney nickel overnight, and isolating 0.75 g (99% of theory) of *N*-methylphenylacetamide from the reaction mixture. After two recrystallizations from cyclohexane the material melted at 58–59° (lit.[9] mp 58°) and its ir and NMR spectra agreed with those in the literature.[10]

Dihydro-4-methyl-6-phenyl-2*H*-1,3,4-thiadiazine-2,5(6*H*)-dione. This preparation was carried out by the same procedure for hydrolyzing **5** to **6**, but with 2 *N* hydrochloric acid. The crude product (0.25 g, 16% of theory) was recrystallized from ethanol three times and then melted at 146°: ir (KBr) 3240, 1760, 1690, 1500, 1450, 1360, 1170, 1130, 1085, 870, 730, and 695 cm^{-1}; NMR (F_3CCOOH) δ 11.0 (s, protons of solvent and –NH–), 7.29 (s, 5, Ph), 5.47 (s, 1, >CH–), 3.05 (s, 3, $-CH_3$).

Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.54, N, 12.60; S, 14.43. Found: C, 53.88; H, 4.60; N, 12.69; S, 14.22.

Hydrolysis of Compounds 5 and 7 to 5-Phenyl-2,4-thiazolidinedione. This was accomplished by refluxing 1.5 g of **5** or **7** with 25 ml of 20% hydrochloric acid for 3 hr and allowing the reaction mixture to slowly cool to room temperature. On chilling, 1 g (85% of theory) of 5-phenyl-2,4-thiazolidinedione was obtained and recrystallized from aqueous ethanol: mp 126–128.5° (lit.[2] mp 129°); ir identical with that in ref 2; NMR (DMSO) δ 12.2 (s, 1, –NH–), 7.45 (s, 5, Ph), 5.7 (s, 1, >CH–).

Evaporation to dryness of the mother liquors from the hydrolysis reaction mixture followed by addition of aqueous sulfuric acid and methanol gave hydrazine sulfate and methyl hydrazine sulfate precipitates, which were identified by their melting points and ir spectra.

5-Phenyl-2,4-thiazolidinedione 2-Isopropylidenehydrazone. Acetone Derivative of 4. This was obtained by allowing **4**, formed along with **5** (see preparation of **5** above), to react with acetone; it was also prepared directly from phenyl(trichloromethyl)carbinol and acetone thiosemicarbazone.

A. Accompanying Preparation of 5. After **5** was filtered off in the preparation given above, the mother liquor was extracted twice with ether and this operation was repeated after the solution was made neutral and also strongly acid. The aqueous layer was then neutralized and filtered, and acetone was added. A precipitate gradually formed; after 10 days 7 g (9% of theory) of the 5-phenyl-2,4-thiazolidinedione 2-isopropylidenehydrazone was obtained, mp 195–200°. Several recrystallizations from 95% ethanol raised the melting point to 201–202° (lit.[11] mp 198–199°). The ir and NMR spectra were identical with those of a pure sample prepared as described immediately below.

B. From Acetone Thiosemicarbazone (8a). To a solution of 31.5 g (0.24 mol) of acetone thiosemicarbazone and 45.1 g (0.2 mol) of phenyl(trichloromethyl)carbinol in 250 ml of ethylene glycol was added a solution of 70 g (1.07 mol) of potassium hydroxide pellets in 200 ml of ethylene glycol over a period of 50 min while the temperature was maintained at 47–50°. The flask was kept at 45° for an additional 2 hr and then allowed to slowly cool to room temperature. The insoluble potassium chloride (26 g) was filtered off, and the solution was diluted with an equal volume of ice and water and extracted with 600 ml of ether. The aqueous solution was chilled to 0°, the pH was adjusted to 7, and the mixture was chilled overnight. There was obtained 31 g (63% of theory) of material, mp 201°. Recrystallization from aqueous ethanol gave 27 g of pure 5-phenyl-2,4-thiazolidinedione-2-isopropylidenehydrazone: mp 201–202° (lit.[11] mp 198–199°); ir (KBr) 3145, 3070–3000, 2930, 2815, 1720, 1640, 1620, 1500, 1460, 1430, 1350, 1260, 1240, 1170, 1075, 870, 800, 760, 725, 690, 675, 570, and 545 cm^{-1}; NMR (DMSO) δ 11.9 (broad s, 1, –NH–), 7.53 (s, 5, Ph), 5.48 (s, 1, >CH–), 2.07 and 2.04 [two s, 6, $=C(CH_3)_2$].

5-Phenyl-2,4-thiazolidinedione 2-benzylidenehydrazone (8b) was prepared in 69% yield from benzaldehyde thiosemicarba-

zone by the same procedure as for **8a**: mp 266–268° (lit.[11,12] mp 257°, 260–261°); NMR (DMSO) δ 12.2 (broad s, 1, –NH–), 8.44 (s, 1, PhCH=N–), ten protons of two phenyl rings gave signals at 7.8–7.7 (m), 7.50 (s), and 7.42 (s), 5.52 (s, 1, PhCHS–).

Anal. Calcd for $C_{16}H_{13}N_3OS$: C, 65.07; H, 4.44; N, 14.23; S, 10.86. Found: C, 65.08, H, 4.65; N, 14.50; S, 11.08.

5-(*p*-Chlorophenyl)-2,4-thiazolidinedione 2-isopropylidenehydrazone (8c) was prepared in 79% yield from *p*-chlorophenyl(trichloromethyl)carbinol[13] as above: mp 227°; NMR (DMSO) δ 12.0 (broad s, 1, –NH–), 7.51 (s, 4, Ph), 5.47 (s, 1, >CH–), 3.73 and 3.71 (s, 6, $-CH_3$).

Anal. Calcd for $C_{12}H_{12}N_3OSCl$: C, 51.15; H, 4.29; N, 14.91; Cl, 12.58. Found: C, 51.42; H, 4.56; N, 14.74; Cl, 12.80.

5-(*p*-Methoxyphenyl)-2,4-thiazolidinedione 2-isopropylidenehydrazone (8d) was prepared in 31% yield from *p*-methoxyphenyl(trichloromethyl)carbinol[13] as above. The material did not melt sharply; after repeated crystallization from aqueous ethanol, it melted at 169–175° when inserted in the melting point bath at 165° and the temperature raised at 2°/min: NMR (DMSO) δ 11.8 (broad s, 1, –NH–), 7.4–6.9 (quartet, 4, Ph), 5.35 (s, 1, >CH–), 3.82 (s, 3, $-OCH_3$), 2.07 and 2.03 (s, 6, $-CH_3$).

Anal. Calcd for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45; N, 15.15; S, 11.56. Found: C, 56.45; H, 5.54; N, 15.05; S, 11.28.

4-Hydroxy-2-methyl-5-phenylthiazole (11). To a solution of 45 g (0.2 mol) of phenyl(trichloromethyl)carbinol and 30 g (0.38 mol) of thioacetamide in 250 ml of ethylene glycol was added 70 g (1.06 mol) of potassium hydroxide pellets in 200 ml of ethylene glycol over an 80-min period at 50°. The mixture was maintained at 50° for an additional 2.5 hr and stirred overnight while cooling to room temperature. The potassium chloride was filtered off, the filtrate and methanol washings were diluted with an equal volume of ice water and extracted with ether to remove neutral material, and the pH of the aqueous solution was adjusted to 9 with hydrochloric acid. The product which precipitated (7.1 g, mp 206–209°, 18% yield) was recrystallized twice from benzene and then weighed 3.3 g and melted at 210–212.5° (same melting point procedure as for **8d**): ir (halocarbon and Nujol oil mulls) 3100–2900, 2700–2000, 1580, 1450, 1425, 1230, 1190, 1030, 995, 865, 755, and 685 cm^{-1}; NMR (DMSO) δ 11.2 (broad s, 1, –OH), 7.8–7.1 (m, 5, Ph); NMR (F_3CCOOH) δ 7.50 (s, 5, Ph), 2.86 (s, 3, $-CH_3$).

Anal. Calcd for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.32; S, 16.77; mol wt, 191. Found: C, 62.92; H, 4.64; N, 7.05; S, 16.80; mol wt (Rast), 182 and 211.

Compound **11** was hydrolyzed by refluxing 0.9 g with 16 ml of aqueous 25% potassium hydroxide for 18 hr. The solution was acidified to pH 7.5 and filtered. An intense purple color developed on adding 3 drops of 5% ferric chloride to the aqueous solution. Air was blown through the solution at room temperature for 3 hr until the purple color was discharged. Dithiobis(phenylacetic acid), mp 208–211°, was isolated which was identical in all respects with an authentic sample.

4-Acetoxy-2-methyl-5-phenylthiazole was prepared by refluxing 1 g of **11** with 10 ml of acetic anhydride for 1 hr. The excess reagents were removed by distillation at 10 mm, and the acetoxythiazole (1 g, 82% of theory) was then distilled, bp 184–190° (10 mm), mp 72–77°. The distillate solidified, and crystallization from ethanol–water raised the melting point to 82°: ir (halocarbon and Nujol oil mulls) 1770, 1540, 1490, 1445, 1375, 1320, 1305, 1275, 1250, 1190, 1040, 1030, 1000, 870, 765, 690, 585, 565, and 550 cm^{-1}; NMR (CCl_4) δ 7.3 (m, 5, Ph), 4.25 (s, 3, ring $-CH_3$), 3.87 (s, 3, acetate $-CH_3$).

Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.76; H, 4.75; N, 6.03; S, 13.74. Found: C, 61.95; H, 5.00; N, 6.12; S, 13.45.

Registry No.—**1**, 2000-43-3; **4**, 55073-89-7; **5**, 55073-90-0; **6**, 55073-91-1; **7**, 55073-92-2; **8a**, 55073-93-3; **8b**, 55073-94-4; **8c**, 55073-95-5; **8d**, 55073-96-6; **11**, 55073-97-7; thiosemicarbazide, 79-19-6; dihydro-4-methyl-6-phenyl-2*H*-1,3,4-thiadiazine-2,5(6*H*)-dione, 55073-98-8; 5-phenyl-2,4-thiazolidinedione, 4695-17-4; acetone thiosemicarbazone, 1752-30-3; benzaldehyde thiosemicarbazone, 1627-73-2; *p*-chlorophenyl(trichloromethyl)carbinol, 5333-82-4; *p*-methoxyphenyl(trichloromethyl)carbinol, 14337-31-6; 4-acetoxy-2-methyl-5-phenylthiazole, 55073-99-9.

References and Notes

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Synthesis of *p*-Methylthiobenzyl Chloride. A Case of Isomer Control in an Electrophilic Substitution[1]

Seemon H. Pines,* Robert F. Czaja, and N. Lee Abramson

Merck Sharp & Dohme Research Laboratories, A Division of Merck & Co., Inc., Rahway, New Jersey 07065

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Reaction of thioanisole and methylal with ~2 mol of aluminum chloride under mild Friedel–Crafts conditions yields 74% *p*-methylthiobenzyl chloride (**1**) accompanied by only ~0.5% of its ortho isomer. Both the yield and isomer ratio change dramatically when 1 mol of aluminum chloride is used. The effect of weaker Lewis acids is reported, and the combined results are rationalized in terms of a mechanism where a thioanisole–Lewis acid complex is proposed as a key to the unique results.

We have devised a superior, direct synthesis of *p*-methylthiobenzyl chloride (**1**) via a new chloromethylation of thioanisole. Besides its immediate practical value,[2] the reaction study provides new information on the behavior of thioanisole in Friedel–Crafts chemistry.[3] For this reason, some of our developmental observations and conclusions are included in this paper.

The title compound is reported to be formed in 23% yield from the chloromethylation of thioanisole with chloromethyl methyl ether[4] in acetic acid.[5] Our scrutiny of that reaction by vapor phase chromatography shows about a 4.5:1 ratio of **1** and its isomer, *o*-methylthiobenzyl chloride (**2**), which are not practicably separable. Attempted monochloromethylation with aqueous formaldehyde and hydrochloric acid gave an even poorer isomer ratio, 7:4.[6] Apparently, the most satisfactory authenticated preparation of **1** is a multistep procedure involving lithium aluminum hydride reduction of *p*-methylthiobenzoic acid, followed by