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Studies on 4-Thiazolidinones. IX.[1] The Conversion of 5-Substituted 2-Thioxo-4-thiazolidinones into Corresponding 2,4-Thiazolidinediones

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Synopsis. The thioxo to oxo conversion in a variety of 2-thioxo-4-thiazolidinones **1** and **2** has been achieved simply by treating with bromine. A postulate for the route of interconversion is given and structures of all products are evidenced by analytical and spectral data.

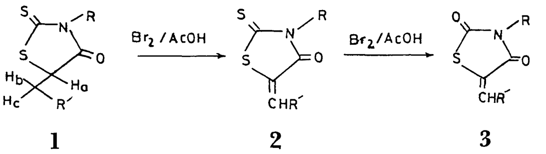
Several methods have been used to effect the thioxo to oxo conversion in 2-thioxo-4-thiazolidinones. Thus, chloroacetic acid in aqueous solution[2] and hydrogen peroxide[3] were used successfully with 2-thioxo-4-thiazolidinone and its 5-alkylidene derivatives. However, the insolubility of many aryl-substituted 2-thioxo-4-thiazolidinones in aqueous chloroacetic acid prevents its use to effect the required transformation.[4] Furthermore, hydrogen peroxide may further oxidize the formed 2,4-dione into sulfoxides, sulfones, and even to sulfate ion.[3,5] The thioxo to oxo conversion has been achieved in 5-arylmethylene-2-thioxo-4-thiazolidinones via two step processes involving first conversion into 2-alkylthio-,[6] 2-(disubstituted amino)[7] 2-thiazolin-4-ones or 2-arylimino-4-thiazolidinones,[6] then treating the product with a hydrolyzing agent.[6,8] The use of the two-step method is somewhat limited as the first step affords mixture of products.

Now, we report an easy method for the conversion of aryl-substituted 2-thioxo-4-thiazolidinones into corresponding 2,4-thiazolidinediones. The reaction is carried out by treating the thioxo compound with bromine in 90% acetic acid solutions. The versatility of this method is illustrated by the successful results obtained upon application on a variety of 2-thioxo derivatives comprising 5-aroylmethyl-3-benzyl-, (*E,Z*)-5-aroylmethylene-3-benzyl-, 5-aroylmethyl- and (*E,Z*)-5-arylmethylene-2-thioxo-4-thiazolidinones (compounds **1a**—**e** and **2a,b,f,g**). Thus, refluxing the acetic acid solutions of **1a** and **2a** and of **1b** and **2b** with bromine for 2h gives 5-benzoylmethylene- and 5-(4-methylbenzoylmethylene)-3-benzyl-2,4-thiazolidinediones (**3a** and **3b**), respectively. The reaction of the 3-unsubstituted derivatives **1c**—**g** with bromine is faster than with the 3-benzyl counterparts and the reaction is completed after warming for 5 min in the case of **1c,d,e** and 15 min in the case of **2f,g**, affording the 2,4-diones **3c,d,e** and **3f,g**, respectively. However, treatment of **1c,d** with bromine at room temperature yielded 5-benzoylmethylene- and 5-(4-methylbenzoylmethylene)-2-thioxo-4-oxo-1,3-thaizolidinones, respectively. This latter method represents a new route to synthesize the hitherto unknown 5-aroylmethylene-2-thioxo-4-thiazolidinones **2c,d**.

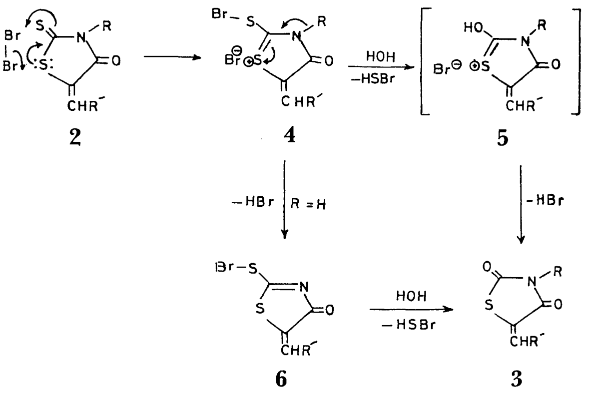
Conversion of **1** into **3** has occurred, most probably, via the dehydrogenated product **2** since it has been reported that **2a** is formed upon treating **1a** with bromine for 5 min.[9] This is supported chemically by the independent transformation of **2a** and **2b** into **3a** and **3b**, respectively.

The structures of **3f,g** are based exclusively on comparsion (mp and IR) with authentic samples[10,11] and that of **3c** is rigidly confirmed by identity (mp and IR) with the (*E*)-isomer isolated from the (*E,Z*)-mixture obtained upon treating 2,4-thiazolidinedione with phenylglyoxal. The structures of **3a,b,c,d,e,g** and **2c,d** are deduced from analytical data and infrared spectra. All the spectra of **3** show the complex carbonyl pattern extending to 1745 cm^{-1} consistent with the stretching vibrations of coupled carbonyl groups and those of **2** show one carbonyl group stretching vibration at ca. 1680 cm^{-1}. Moreover, compounds **2** give the color reaction reported previously by Turkevich et al.[12] to characterize the 2-thioxo-4-thiazolidinones.

The problem of configurational assignment to **2c** and **3c,f,g** has been solved by ^{1}H NMR spectroscopy. The (*E*)-configuration has conferred to **2c** and **3c** as they are identical with the (*E*)-isomers isolated from



a R=CH_2Ph; R′=C_6H_5CO
b R=CH_2Ph; R′=4-CH_3-C_6H_4CO
c R=H; R′=C_6H_5CO
d R=H; R′=4-CH_3-C_6H_4CO
e R=H; R′=4-Br-C_6H_4CO
f R=H; R′=C_6H_5
g R=H; R′=4-CH_3O-C_6H_4



Scheme 1.

Table 1. Some Data of the Newly Synthesized Compounds

Compd No.	Mp	Yield	Formula[q]	¹H NMR Spectral data					
	°C	%		Olefinic hydrogen	Aromatic hydrogen[k]		N-CH_2Ph	CH_3	Exchangable H
1b	137—138[a]	70	$C_{19}H_{17}NO_2S_2$						
1c	164—165[b]	65	$C_{11}H_9NO_2S_2$						
1d[j,l]	172—173[b]	60	$C_{12}H_{11}NO_2S_2$	—	7.85 d, 2H	7.30 d, 2H	—	2.45 s	9.30 br s
1e	192—193[b]	70	$C_{11}H_8BrNO_2S_2$						
2b	215—217[c]	90(90)[g]	$C_{19}H_{15}NO_2S_2$	7.85 s	7.88 d, 2H	7.35—7.05 m, 7H	5.30 br s	2.23 s	—
(*E*)-**2c**[p]	284—286[d]	85	$C_{11}H_7NO_2S_2$	7.85 s	8.10 dt, 2H	7.62 m, 3H	—	—	3.50 br s
(*Z*)-**2c**	236—238[e]	—	$C_{11}H_7NO_2S_2$	7.93 s	8.16 dt, 2H	7.62 m, 3H	—	—	3.57 br s
2d	254—255[c]	85	$C_{12}H_9NO_2S_2$	7.95 s	7.80 d, 2H	7.25 d, 2H	—	2.30 s	3.10 br s
3a	157—159[a]	85(83)[h]	$C_{18}H_{13}NO_3S$	8.13 s	8.03 dt, 2H	7.20—7.70 m, 8H	4.80 br s	—	—
3b	154—155[a]	80(80)[h]	$C_{19}H_{15}NO_3S$	8.20 br s	8.00 d, 2H	7.60 d, 7H	4.80 br s	2.32 s	—
(*E*)-**3c**	219—221[a]	90	$C_{11}H_7NO_3S$	7.82 s	8.10 m, 2H	7.60—7.80 m, 3H	—	—	7.50 br s
(*Z*)-**3c**	202—203[f]	—	$C_{11}H_7NO_3S$	8.03 s	8.10 dt, 2H	7.55 dt, 3H	—	—	3.25 br s
3d	219—220[c]	85	$C_{12}H_9NO_3S$						
3e	250—252[c]	90	$C_{11}H_6BrNO_3S$	7.95 s	8.00 d, 2H	7.70 d, 2H	—	—	3.25 br s
(*E, Z*)-**3f**	238—239[c]	75(70)[i]	$C_{10}H_7NO_2S$	7.85[m] s 7.75[m] s	7.10 br s, 5H		—	—	11.80 br s
(*E, Z*)-**3g**	211—212[c]	80(78)[i]	$C_{11}H_9NO_3S$	7.80[n] s 7.75[n] s	7.55 d, 2H	7.07 d, 2H	—	3.90[n,o] s 3.80[n,o] s	12.40 br s

a) Glacial acetic acid. b) Methanol. c) Toluene. d) Dioxane. e) 1-Butanol. f) Benzene. g) Yield obtained upon treating **1b** with one molar proportion of bromine. h) Yields obtained upon treating **2a** and **2b** with 1 or 2 molar proportions of bromine. i) Yields obtained upon treating **3f** and **3g** with one molar proportion of bromine. j) Measured in $CDCl_3$. k) All aromatic d show J=7.0 Hz. l) The spectrum shows also the following signals: δ=4.75 (dd, H_a), 3.95 (dd, H_c), 3.60 (dd, H_b). J_{H_a,H_b}=9.0 Hz, J_{H_a,H_c}=3.50 Hz, J_{H_c,H_b}=1.8 Hz. m) Characteristic of (*Z*)- and (*E*)-isomers with the integrated proton ratios of 3:7, respectively. n) Characteristic of (*Z*)- and (*E*)-isomers with the integrated proton ratios of 1:9 respectively. o) The methoxyl proton signal. p) ¹³C NMR (DMSO-d_6) δ=200.5 (s), 187.7 (s), 168.7 (s), 144.0 (s), 135.9 (s), 133.9 (d), 128.8 (d), 128.5 (d), 116.4 (d). q) Satisfactory analytical data (within 0.3% for C, H, and N) were obtained for all new compounds.

the (*E,Z*)-mixtures obtained upon condensing 2-thioxo-4-thiazolidinone and 2,4-thiazolidinedione with phenylglyoxal. However, **3f,g** are (*E,Z*)-mixtures and integrated proton ratios show that the (*Z*)-isomers constitute 10% and 30%, respectively. The (*E*)- and (*Z*)-configurations are deduced by comparing the observed chemical shift values of the exocyclic olefinic protons with the incremented values.[13] The olefinic proton is relatively deshielded in the (*Z*)-rather than the (*E*)-isomers.

The thioxo to oxo conversion may be visualized to occur via the route represented in Scheme 1. The possibility of formation of **3** via the action of water on 5-aroylmethylene-2-bromothio-2-thiazolin-4-one (**6**) which is believed to be formed via elimination of hydrogen bromide directly from **4**, in compounds having no substituents at the 3-position, cannot be ruled out, especially that easy displacement of the 2-alkylthio group by nucleophiles in similar systems has been reported.[6] A chemical support for the formation of **4** is gained from the isolation of semisolids containing bromine upon treating **1a** and **2g** with bromine in chloroform. Formation of sulfonium salts is well-known upon treating sulfides with N-halo amides, but to our knowledge, formation of it upon treating with bromine is not reported.

The 5-aroylmethyl- and 5-aroylmethyl-3-benzyl-2-thioxo-4-thiazolidinones **1b**—**e** are synthesized by treating the respective 3-aroylacrylic acids[15] with ammonium dithiocarbamate and benzyl dithiocarbamate.

The structures of **1b**—**e** are based on microanalysis, infrared and ¹H NMR spectroscopy. The structures of **2a,b** are based on analytical and infrared spectral data which show the stretching absorptions consistent with ketonic and amidic C=O groups.

Experimental

All melting points are uncorrected. IR spectra were measured on a Unicam SP 1200 spectrometer as KBr discs. ^{1}H NMR were recorded in DMSO-d_6 on a Varian EM 390, 90 MHz instrument except those of **2c** which were recorded on a JEOL FX-900, 90 MHz apparatus, using TMS as an internal standard with chemical shifts (δ) expressed in ppm downfield from it. ^{13}C NMR was recorded on a JEOL FX-900, 22.5 MHz instrument. Mass spectrum was measured on a Varian MAT SM 1 spectrometer. The term acetic acid used herein refered to a 90% (v/v) solution.

Starting Materials. The following compounds were prepared as described previously: 5-Benzoylmethyl-3-benzyl-2-thioxo-4-thiazolidinone (**1a**).[9] 5-Benzoylmethylene-3-benzyl-2-thioxo-4-thiazolidinone (**2a**).[9] 5-Benzylidene-2-thioxo-4-thiazolidinone (**2f**).[16] 5-(4-Methoxybenzylidene)-2-thioxo-4-thiazolidinone (**2g**).[17]

5-(4-Methylbenzoylmethyl)-3-benzyl-2-thioxo-4-thiazolidinone (1b) and 5-Aroylmethyl-2-thioxo-4-thiazolidinones (1c—e). A solution of ammonium benzyldithiocarbamate or ammonium dithiocarbamate (10 mmol) in ethanol (10 ml) was added to a stirred solution of 3-benzoyl-, 3-(4-methylbenzoyl)- or 3-(4-bromobenzoyl) acrylic acid (10 mmol) in ethanol (10 ml) at room temperature. Stirring was continued for 30 min, then concentrated hydrochloric acid (3.0 ml) was added in three portions during 30 min and the pale yellow solid prepicipitated after stirring for 2 h was filtered off, washed successively with water, dried and recrystallized from the proper solvent to give the title compounds.

Conversion of 1c,d into 2c,d. Bromine (20 mmol) was added to a solution of each of **1c,d** (10 mmol) in acetic acid (20 ml) and the mixture left to stand at room temperature for 1 h during which hydrogen bromide gas evolved. The reaction mixture was poured into cold water and the precipitated solid was filtered off, washed several times with cold water, dried and recrystallized from the proper solvent to give the respective **2c,d**

Conversion of 1b into 2b. A solution of **1b** (10 mmol) in glacial acetic acid (20 ml) was heated with bromine (10 or 20 mmol) for 5 min. The reaction mixture was treated with charcoal, concentrated and the faint yellow crude product was recrystallized from toluene to give 5-(4-methylbenzoylmethylene)-3-benzyl-2-thioxo-4-thiazolidinone (**2b**).

5-Aroylmethylene-3-benzyl- (3a,b), 5-Aroylmethylene- (3c,d,e), and 5-Arylmethylene-2,4-dioxo-1,3-thiazolidinediones (3f,g). A solution of **1** (10 mmol) or **2** (10 or 20 mmol) in acetic acid (20 ml) was heated with bromine (20 mmol) for the time required. The reaction mixture was treated with charcoal, concentrated and the pale yellow crude product was filtered off, washed several times with small portions of ice-cold diethyl ether and dried.

Compounds **1a** and **2a** and **1b** and **2a** were refluxed for 2 h and afforded **3a** and **3b**, respectively.

Compounds **1c,d,e** were refluxed for 5 min and gave **3c,d,e** respectively.

Compounds **2f,g** were refluxed for 15 min and gave **3f,g** respectively.

Synthesis of Authentic Samples. A mixture of 2,4-thiazolidinedione or 2-thioxo-4-thiazolidinone (10 mmol), phenylglyoxal (10 mmol), anhydrous sodium acetate (30 mmol), and glacial acetic acid (50 ml) was refluxed for 40 min. The reaction mixture was poured into ice-cold water and the precipitated solid was filtered off, washed successively with water and dried. The faint brown crude product (80%) melted at 200—205 °C obtained from 2,4-thiazolidinedione is found to be a mixture of the (Z)- and the (E)-isomers in the ratio of 1:9, respectively, by ^{1}H NMR spectroscopy. Separation of the isomers was attained by dissolving the crude product in glacial acetic acid and allowing to stand overnight. The faint brown crystals which separated are filtered off and recrystallized from glacial acetic acid to give (E)-5-benzoylmethylene-2,4-thiazolidinedione (**3c**), 90%.

Dilution of the original mother liquor with water precipitated a faint brown solid which was recrystallized from benzene to give the (Z)-isomer 10%.

The crude yellowish brown product (80%), mp 214—220 °C obtained from 2-thioxo-4-thiazolidinone was found to be a mixture of (Z)- and (E)-5-benzoylmethylene-2-thioxo-4-thiazolidinones (**2c**) in the ratio of 3:7, respectively, as evidenced by ^{1}H NMR spectroscopy. The fraction which precipitated upon allowing the 1-butanol extract to cool was filtered off and recrystallized from 1-butanol to give (Z)-**2c** 30%.

The insoluble fraction was recrystallized from dioxane to give (E)-**2c** 70%.

Reactions of 1a and 2g with Bromine in Chloroform. A mixture of **1a** or **2g** (5 mmol), bromine (10 mmol) and chloroform (20 ml) was refluxed for 3 h. Evaporation of the solvent using rotary evaporator left a viscous oil. Trituration with light petroleum (bp 40—60 °C) followed by recrystallization from toluene failed to give a pure praduct. The faint yellow crystals obtained upon dissolution in 90% acetic acid solution was filtered off, dried and recystallized from glacial acetic acid.

Compound **1a** gave a product (70%) identical (mp and IR) with **3a**.

Compound **2g** afforded **3g** (70%), identical (mp and IR) with an authentic sample.[11]

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