The Route of Action of Sodium Methoxide on 5-Arylmethylene-2-Disubstituted Amino-4-oxo-2-thiazolines

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5-Arylmethylene-2-disubstituted amino-4-oxo-2-thiazolines **1a-d** reacted with six and two moles of sodium methoxide to give the 2-mercaptocinnamic acid esters **6** and mixtures of 2,2-dimethoxy-4-oxothiazolidines **4** and 2,4-dioxothiazolidines **5**, respectively. The intermediate mixture of the sodium salt of 5-arylmethylene-2,2-dimethoxy-4-oxothiazolidines **3** in the above mentioned transofrmations was established. The structures of **3**, **4**, **5** and **6** were based on analytical and spectral evidence. The route of conversion of **1** into **3**, **4**, **5** and **6** was presented and discussed.

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In continuation of our work (1,2,3) on the chemistry of thiazolinones, we now report the reaction of these compounds with sodium methoxide. It has been observed that, 5-arylmethylene-2-disubstituted amino-4-oxo-2-thiazolines **1a-d** react with six and two moles of sodium methoxide to give the 2-mercaptocinnamic acid esters **6** and mixtures of 5-arylmethylene-2,2-dimethoxy-4-oxothiazolidines **4** and 5-arylmethylene-2,4-dioxothiazolidines **5**, respectively. The synthesis of **6** has been reported earlier by other methods (4,5,6). However, the synthesis of **4** has not been published.

Thus, refluxing a methanol solution of **1a** or **1c** with six moles of sodium methoxide gives the methyl 2-mercaptocinnamate **6a**. Similar treatment of **1b** or **1d** affords the methyl 2-mercapto-4-methoxycinnamate **6b**.

The structure of **6a** is based exclusively on comparison (mp and ir) with an authentic sample (4). The structure of **6b** is based on analytical data, infrared and ^{1}H nmr spectra and supported by the ease of oxidation with an ethereal solution of iodine to the disulphide **7**.

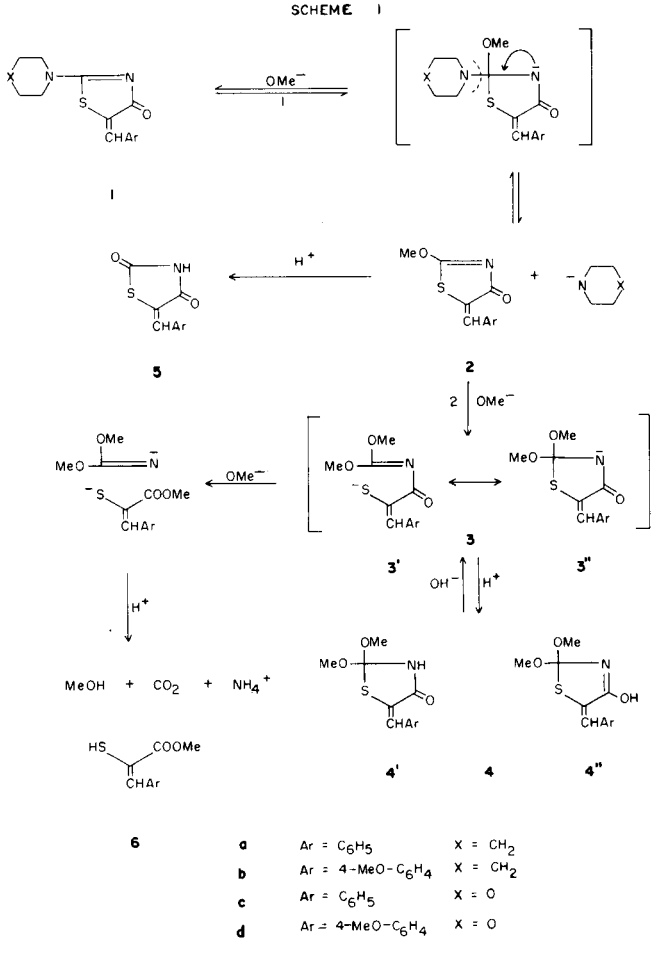
However, treating the methanol solution of **1a** or **1c** with two molar porportions of sodium methoxide and neutralizing the reaction mixture to *p*H 4 affords a mixture of 5-benzylidene-2,2-dimethoxy-4-oxothiazolidine **4a** and 5-benzylidene-2,4-dioxothiazolidine **5a**. Similar treatment of **1b** or **1d** gives a mixture of **4b** and **5b**.

The structure of **4a** and **4b** is confirmed by analytical and spectral data. In the solid state, it seems that these compounds exist as mixtures of the tautomers **4'** and **4''**, as evidenced by the detection of NH and OH as well as C=O and C=N group stretching frequencies in the infrared spectra when dispersed in mineral oil. In dimethylsulfoxide solution, however, the ^{1}H nmr spectra of **4** exhibits a broad absorption at δ 0.85 ppm and show the olefinic and the hetero-ring methoxyl singlets in the ratio of 1:6 which support the existence of these compounds mostly as **4'** rather than **4''**.

The structure of **5a** and **5b** is based exclusively on comparison (mp and ir) with authentic samples (8,9).

The route of action of alkoxides on the thiazolinones **1** may be assumed to proceed as follows: an addition elimination reaction involving the alkoxide ion and the C=N group of **1** affords the 2-methoxythiazolinones **2**, which add another molecule of alkoxide to give the anions of the

SCHEME I



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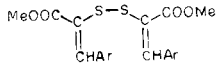
dimethoxy derivatives **3**. Further action of the alkoxide ion on **3** will lead to the conversion into **6** (*cf.* Scheme I). The easy addition of Grignard reagents to the C=N group of **1** (2) is in accord with the nucleophilic additions presented in steps 1 and 2, and the easy conversion of the 2-alkylthio analogues of **2** into **1** (1) is consistent with the reversibility of the intervening steps. The intermediacy of the sodium salts **3** through the conversion of **1** into **4** and **6** is evidenced on the one hand by the successful isolation of **3b** on treating the 2-piperidino-**1b** and the 2-morpholino-**1d**-4-oxo-2-thiazolines with two moles of sodium methoxide and by the easy conversion of **3b** into **6b** through the reaction with alkoxides. In methanol solutions, it seems that compounds **3** exist as a resonance hybrid between the two canonical structures **3'** and **3''**, as evidenced by the ^{1}H nmr spectrum of **3b** (deuteriomethanol) which shows from low to high field the signals of olefinic (singlet), aromatic (two doublets), hetero-ring methoxyl of **3'** (singlet), aromatic ring methoxyl (singlet) and hetero-ring methoxyl of **3''** (singlet), with the integrated proton areas of 1:2:2:3:3:3, respectively.

Formation of the 2,4-dioxothiazolidines **5** may be supposed to occur through the hydrolysis of the 2-methoxythiazolinones **2** during the neutralization step. A similar behaviour was reported for the 2-alkylthio analogues of **2** (1).



7 Ar = 4-MeO-C_6H_4

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were measured on a Perkin-Elmer 475 spectrophotometer using the Nujol mull technique. Nmr spectra were recorded on a Bruker 80 MHz instrument using tetramethylsilane as an internal standard with chemical shifts (δ) expressed in ppm downfield from TMS. The 5-arylmethylene-2-disubstituted amino-4-oxo-2-thiazolines used herein were synthesised earlier in our laboratories (1,7).

Methyl 2-Mercaptocinnamates (**6a-b**).

Powdered **1a**, **b**, **c** or **d** (0.005 mole) was added to a solution of sodium methoxide (0.03 mole) in 100 ml of methanol and the whole mixture was refluxed for 3 hours, then concentrated, cooled, poured into ice-cold water, acidified with dilute sulphuric acid solution and extracted with ether. The ether insoluble fraction was filtered off, dried and recrystallized from methanol to give **1a**, **b**, **c** or **d** (5.0-7.0%), as evidenced by mp and mixture mp with the starting thiazolinones. The ethereal layer was washed several times with water, dried with sodium sulphate and evaporated to an oil.

The oils obtained from **1a** and **1c** were triturated several times with light petroleum (bp 40-60°) and the semi-solids thus obtained were recrystallized from the same solvent to give methyl 2-mercaptocinnamate, **6a** (~70%), mp 42-43°, identical (mp and ir) with an authentic sample (4).

The oils obtained from **1b** and **1d** were chromatographed over silica gel and eluted with ether-light petroleum (bp 40-60°) mixture (1:4 v/v) to give methyl 2-mercapto-4-methoxycinnamate **6b** (~73%), mp 38-40°; ir: 1690 cm^{-1} (C=O); nmr (deuteriochloroform): δ 7.75 (s, olefinic, 1H), 5.7-7.0 (m, aromatic, 4H), 4.7 (s, thiol, 1H), 3.82 (s, methoxycarbonyl, 3H), 3.80 (s, aromatic methoxyl, 3H).

Anal. Calcd. for $C_{11}H_{12}O_3S$: C, 58.92; H, 5.35; S, 14.28. Found: C, 58.85; H, 5.35; S, 14.30.

Dimethyl 2,2'-Dithio-3,3'-di-(4-methoxyphenyl)diacrylate (**7**).

A solution of **6b** (0.005 mole) in 50 ml of ether was treated portionwise while shaking with a solution of iodine in ether (2.0%) until the appearance of the color of iodine. The white solid which precipitated after allowing the reaction mixture to stand at room temperature for 15 minutes was filtered off, dried and recrystallized from methanol to give **7** (70%), mp 155-157°.

Anal. Calcd. for $C_{22}H_{22}O_6S_2$: C, 59.19; H, 4.93; S, 14.35. Found: C, 59.10; H, 4.85; S, 14.50.

5-Arylmethylene-2,2-dimethoxy-4-oxothiazolidines (**4a-b**) and 5-Arylmethylene-2,2-dioxothiazolidines (**5a-b**).

The mixed solutions of sodium methoxide (0.01 mole) in 50 ml of methanol and each of **1a-d** (0.005 mole) in 50 ml of methanol were heated under reflux for 2 hours. The reaction mixture was concentrated, poured into ice-cold water, stirred with 200 ml of ether and neutralized with a solution of acetic acid to *p*H 4. The ether insoluble fraction was filtered off and recrystallized from methanol to give **1a**, **b**, **c** or **d**, as confirmed by mp and mixture mp with the starting thiazolinones. The ethereal solu tion was washed successively with water, dried over anhydrous sodium sulphate, concentrated to 50 ml, treated with a few drops of light petroleum (bp 40-60°) and refrigerated for 12 hours. The colourless solid which precipitated was filtered off and dried.

The solid obtained from **1a** and **1c** was recrystallized from glacial acetic acid to give 5-benzylidene-2,4-dioxothiazolidine **5a** (10%), mp 243-245°, identical (mp and ir) with an authentic specimen (8).

The solid obtained from **1b** or **1d** was recrystallized from ethanol to give 5-(4-methoxyphenylmethylene)-2,4-dioxothiazolidine **5b** (~10%), mp 214-215°, identical (mp and ir) with an authentic sample (9).

The ethereal layer was evaporated and the faint yellow solid thus obtained was fractionally recrystallized from benzene-ethanol to give the respective 2,2-dimethoxy derivatives.

Compounds **1a** and **1c** afforded 5-benzylidene-2,2-dimethoxy-4-oxothiazolidine **4a** (~70%), mp 238-240°; ir: 3420 cm^{-1} (OH), 3110-3010 cm^{-1} (NH and CH), 1685 cm^{-1} (C=O), 1645 cm^{-1} (C=N); nmr (deuteriodimethylsulfoxide): δ 7.75 (s, olefinic, 1H), 7.675-7.375 (m, aromatic, 5H), 3.25 (s, hetero-ring methoxyl, 6H), 0.85 (broad s, amide, 1H) disappeared on addition of deuterium oxide.

Anal. Calcd. for $C_{12}H_{13}NO_3S$: C, 57.37; H, 5.18; N, 5.57. Found: C, 57.30; H, 5.15; N, 5.55.

Compounds **1b** and **1d** gave 5-(4-methoxyphenylmethylene)-2,2-dimethoxy-4-oxothiazolidine **4b** (~75%), mp 212-214°; ir: 3380 cm^{-1} (OH), 3220-3100 cm^{-1} (NH and CH), 1685 cm^{-1} (C=O), 1635 cm^{-1} (C=N); nmr (deuteriodimethylsulfoxide): δ 7.70 (s, olefinic, 1H), 7.05 (d (J = 9.0 ppm), aromatic, 2H), 7.53 (d (J = 9.0 ppm), aromatic, 2H), 3.80 (s, aromatic methoxyl, 3H), 3.25 (s, hetero-ring methoxyl, 6H), 0.845 (broad s, amide, 1H).

Anal. Calcd. for $C_{13}H_{15}NO_4S$: C, 55.51; H, 5.34; N, 4.98. Found: C, 55.50; H, 5.25; N, 5.10.

Sodium Salt of 2,2-Dimethoxy-5(4-methoxyphenylmethylene)-4-oxothiazolidine (**3b**).

The solutions of sodium methoxide (0.005 mole) in 50 ml of methanol and **1b** (0.005 mole) in 10 ml of methanol were mixed and refluxed for 2 hours. The reaction mixture was concentrated, refrigerated and the yellow clusters which precipitated were filtered off and recrystallized from methanol to give **3b** (40%), mp 300° dec; nmr (deuteriomethanol): δ 7.55 (s, olefinic, 1H), 7.35 (d (J = 9.0 ppm), aromatic, 2H), 6.975 (d (J = 9.0 ppm), aromatic, 2H), 4.18 (s, hetero-methoxyl of **3'**, 3H), 3.77 (s, aromatic ring methoxyl, 3H), 2.65 (s, hetero-ring methoxyl of **3''**, 3H).

Anal. Calcd. for $C_{13}H_{14}NO_4SNa$: C, 51.50; H, 4.60; N, 4.60. Found: C,

51.55; H, 4.55; N, 4.75.

Conversion of **3b** into **6b**.

Powdered **3b** (0.005 mole) was added to a solution of sodium methoxide (0.01 mole) in 100 ml of methanol and the whole mixture was refluxed for 2 hours and worked up as usual. The crude product obtained after acidification of the diluted reaction mixture was triturated several times with light petroleum (bp 40-60°) and the residual semi-solid was recrystallized from the same solvent to give methyl 2-mercaptocinnamate **6b** (73%), mp 38-40°, undepressed on a mixture with the sample previously obtained.

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