A NEW RING TRANSFORMATION OF BENZOTHIAZOLINES TO 3-OXO-2,3-DIHYDRO-4H-1,4-BENZOTHIAZINES OR BENZOTHIAZOLES

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A new ring transformation of benzothiazolines to 3-oxo-2,3-dihydro-4H-1,4-benzothiazines or benzothiazoles was found in the reaction of 2,2-dimethyl- (1) or 2-methyl-2-phenylbenzothiazoline (2) with chloroacetyl chloride.

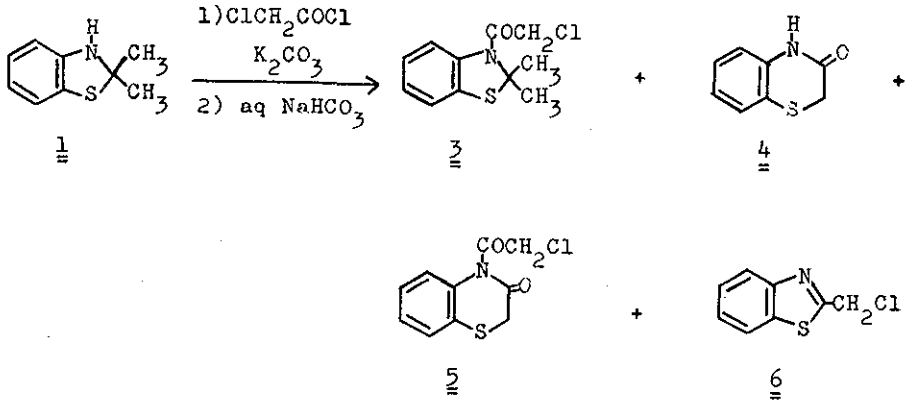
A recent study of the formation of benzothiazine derivatives by the reaction of 2,2-disubstituted benzothiazolines with sulfuryl chloride[1] prompted us to communicate results concerning the new ring transformation of benzothiazolines to 3-oxo-2,3-dihydro-4H-1,4-benzothiazines or benzothiazoles.

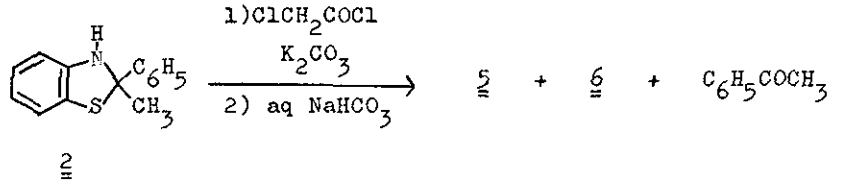
Benzothiazolines are of considerable interest from both synthetic and pharmacological points of view. In our previous publication, we reported the synthesis of benzothiazolines and their hydrolytic or oxidative ring-opening reaction.[2]

Takamizawa, et al. reported the ring expansion of benzothiazolium salts to 3-oxo-2,3-dihydro-4H-1,4-benzothiazines by

use of diethyl acylphosphonate,[3] but the mechanism of the reaction was entirely different from that of our reaction which we wish to describe here.

To a stirred suspension of 2,2-dimethylbenzothiazoline (1) (5 mM) and anhydrous K_2CO_3 (25 mM) in dry ether was gradually added chloroacetyl chloride (25 mM). After stirring for 28 hr





Scheme 1

at room temperature the reaction mixture was treated with aqueous $NaHCO_3$. The products were isolated by the preparative thin layer chromatography (tlc) on silica gel using benzene and

identified as 3-chloroacetyl-2,2-dimethylbenzothiazoline (3, 17 %), 3-oxo-2,3-dihydro-4H-1,4-benzothiazine (4, 11 %), 4-chloroacetyl-3-oxo-2,3-dihydro-4H-1,4-benzothiazine (5, 9 %) and 2-chloromethylbenzothiazole (6, 47 %) by their analytical and spectral data and unequivocal synthesis. Their physicochemical and spectral data were: 3: colorless prisms (EtOH), mp 104-106°C. nmr ($CDCl_3$) δ 1.95 (6H, s, C_2-CH_3), 4.29 (2H, s, CH_2), 7.05-7.35 (4H, m, ArH). ir (KBr) ν cm^{-1} 1660 (CO). 4: colorless needles (EtOH), mp 183-184°C. nmr (CF_3CO_2H) δ 3.63 (2H, s, CH_2), 6.90-7.60 (4H, m, ArH). ir (KBr) ν cm^{-1} 3300 (NH), 1650 (CO). 5: colorless needles (EtOH-hexane), mp 112-113°C. nmr ($CDCl_3$) δ 3.48 (2H, s, C_2-H), 4.85 (2H, s, $COCH_2Cl$), 7.00-7.65 (4H, m, ArH). ir (KBr) ν cm^{-1} 1690 (CO). 6: colorless oil, bp 118-120°C (1.15 mmHg). nmr ($CDCl_3$) δ 4.92 (2H, s, CH_2), 7.20-7.70 (2H, m, ArH), 7.70-8.25 (2H, m, ArH).

The ring transformation products, 5 (36 %) and 6 (25 %) and acetophenone (58 %) were obtained in the case of 2-methyl-2-phenylbenzothiazoline (2), which was supposed to be more reactive than 1 because of the steric effect by phenyl group.

In order to elucidate the mechanism the reaction was closely examined. The nmr spectra of the reaction mixture of 1 and chloroacetyl chloride in $CDCl_3$ showed the peaks at δ 2.43 (3H, s, $=$-CH_3), 2.94 (3H, s, $=$-CH_3), 4.43 (2H, s, CH_2) of S-(2-isopropylideneaminophenyl) thiochloroacetate (8) hydrochloride and these peaks disappeared on addition of aqueous $NaHCO_3$. Moreover, the reaction was carried out in the presence of anhydrous K_2CO_3 and worked up without aqueous $NaHCO_3$ to give N,S-di-

acyl o-aminobenzenethiol (9, 64 %), colorless prisms (EtOH-hexane), mp 80-81°C. nmr ($CDCl_3$) δ 4.18 (2H, s, CH_2), 4.30 (2H, s, CH_2), 7.00-7.75 (3H, m, ArH), 8.20-8.50 (1H, m, ArH), 8.85 (1H, broad s, NH). ir (KBr) ν cm^{-1} 3300 (NH), 1690 (CO), which was identified with an authentic sample synthesized from o-aminobenzenethiol and chloroacetyl chloride. Treatment of 9 with aqueous $NaHCO_3$ gave 5 (24 %) and 6 (72 %). 3-Chloroacetyl-2,2-dimethylbenzothiazoline (3) did not further react with chloroacetyl chloride.

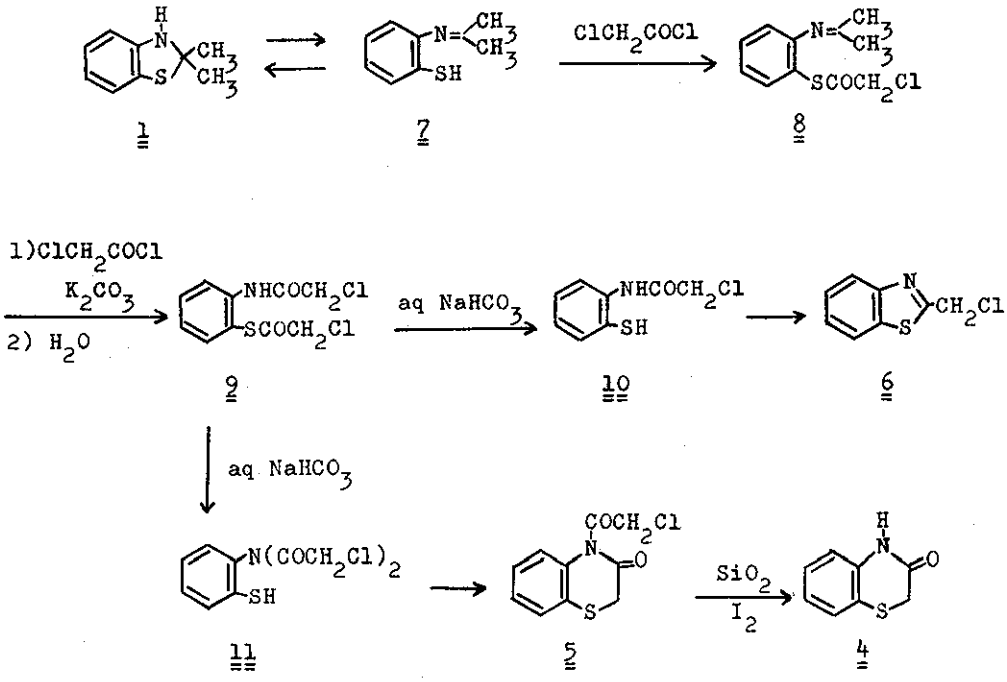
On the basis of these data described above we propose the mechanism for the reaction of 1 and chloroacetyl chloride as shown in Scheme 2.

Tautomerization of 1 forms a Schiff's base (7),[4] which is acylated to S-(2-isopropylideneaminophenyl) thiochloroacetate (8) by chloroacetyl chloride. Acylation and hydrolysis of 8* yields an intermediate 9, which brings about the S→N acyl migration in competition with the hydrolysis of the thiol ester.[5] o-(N,N-Bis-chloroacetylamino)benzenethiol (11) cyclizes to 5 and the other derived from 9, 2-chloroacetamidobenzenethiol (10) is readily dehydrated to 6. The formation of 4 is explained as follows: Chromatography of 5 on silica gel (Wakogel B-10) tlc plates and successive exposure of it to iodine caused dechloroacetylation to give 4. The nmr spectrum of the reaction mixture which was untreated with silica gel and iodine showed no presence of 4. It was concluded that 5 was dechloroacetylated in the course of

* Hydrolysis may be caused by traces of water in dry ether.

See reference 1.

the purification.



Scheme 2

Further related studies directed toward the application to synthetic organic chemistry are also in progress.

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