Rearrangement of a Pyranone to a Benzothiazole

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The conversion of 2-chloromethyl-5-methoxy-4*H*-pyran-4-one to 2-amino-5-hydroxy-6-methoxybenzothiazole hydrochloride under mild reaction conditions has been observed. The synthesis of the identical benzothiazole by an alternate unequivocal method is also reported.

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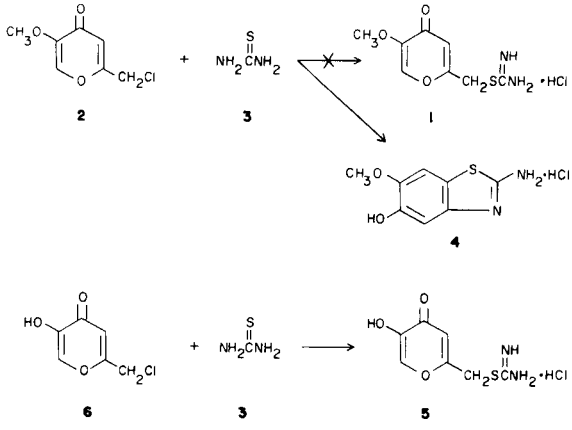
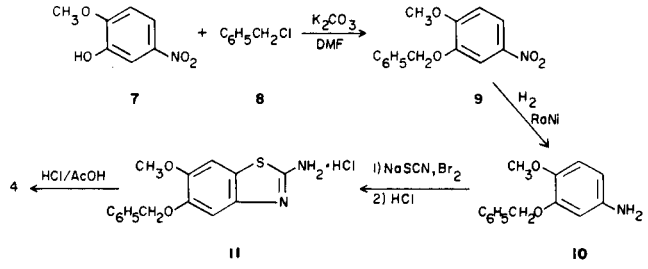
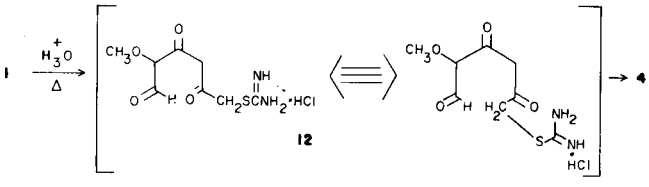
While pursuing another investigation, preparation of the unknown isothiuronium salt **1** was attempted with 2-chloromethyl-5-methoxy-4*H*-pyran-4-one (**2**) and thiourea (**3**). However, the isolated product showed loss of a mole of water by elemental analysis. Also, the expected methylene signal of **1** was not observed by nmr. Assimilation of the spectral data and elemental analysis permitted structural assignment of the product as 2-amino-5-hydroxy-6-methoxybenzothiazole hydrochloride (**4**). No evidence of this type of rearrangement was found in the literature. Preparation of the homologous isothiuronium salt **5** of 2-chloromethyl-5-hydroxy-4*H*-pyran-4-one (chlorokojic acid, **6**) by the literature method (1) proceeded uneventfully, and the nmr spectrum of the product and its elemental analysis supported structure **5** instead of rearrangement to a benzothiazole.



Unequivocal synthesis of the benzothiazole **4** was carried out in the following manner. The hydroxy group of 2-methoxy-5-nitrophenol (5-nitroguaiacol, **7**) was protected by alkylation with benzyl chloride (**8**). The resulting 2-benzyloxy-1-methoxy-4-nitrobenzene (**9**) was smoothly reduced with hydrogen in the presence of Raney nickel catalyst to 3-benzyloxy-4-methoxyaniline (**10**). Treatment of **10** with sodium thiocyanate and bromine permitted isolation of 2-amino-5-benzyloxy-6-methoxybenzothiazole hydrochloride (**11**). Benzothiazole ring formation by this method is a known, general procedure (2). The benzyl group of **11** was cleaved with 3% hydrogen chloride/acetic acid. The ir and nmr spectra of the cleavage product matched the spectra of the rearrangement product **4**. Furthermore, a mixture melting point of the two samples was undepressed. Thus, the structural assignment of **4** as 2-amino-5-hydroxy-6-methoxybenzothiazole hydrochloride was verified by an alternate, unequivocal synthesis.



The rearrangement reaction giving rise to **4** is presumed to occur through the isothiuronium salt **1**. Salt **1** undergoes rapid hydrolysis to the ring-opened product which can be drawn as **12**. Subsequent methylene condensation with the aldehyde moiety of **12** and Schiff base formation to the thiazole then leads to the product **4**.



EXPERIMENTAL

Melting points were taken in a Mel-Temp apparatus in open capillary tubes and are corrected. Nuclear magnetic resonance spectra were taken on a Varian A-60A instrument with TMS as internal standard. Infrared spectra were determined as Nujol mulls with a Perkin-Elmer 137B spectrophotometer.

5-Hydroxy-4*H*-pyran-4-one-2-methylisothiuronium Chloride (**5**).

A mixture of 2-chloromethyl-5-hydroxy-4*H*-pyran-4-one (chlorokojic acid, 4.8 g., 0.030 mole) and thiourea (2.3 g., 0.030 mole) in absolute ethanol (50 ml.) was refluxed 1.5 hours. The solution was cooled, and the resulting solid was collected. Two recrystallizations from absolute ethanol (400 ml.) yielded 1.9 g. (27%) of a tan solid, m.p. 151-152° [lit. (1) m.p. 155°]; ir: ν 6.05 (CO); nmr (DMSO-d_6): δ 9.55 (exchangeables), 8.13

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(s, 1, pyran H), 6.60 (s, 1, pyran H), 4.65 (s, 2, CH_2).

Anal. Calcd. for $C_7H_8N_2O_3S \cdot HCl$: C, 35.52; H, 3.83; N, 11.84. Found: C, 35.30; H, 3.86; N, 11.92.

2-Amino-5-hydroxy-6-methoxybenzothiazole Hydrochloride (**4**).

A mixture of 2-chloromethyl-5-methoxy-4*H*-pyran-4-one (23 g., 0.13 mole) (3) and thiourea (9.9 g., 0.13 mole) was refluxed in 95% ethanol (650 ml.) for 3.0 hours. The solution was concentrated under reduced pressure to *ca.* 400 ml. and allowed to stand overnight to give 12.0 g. of solid. Concentration of the filtrate to 50 ml. yielded another 8.0 g. The combined solids were recrystallized from 95% ethanol to give 19 g. (63%) of title product in two crops, m.p. 282-284°; ir: (benzothiazole C=N) 6.1μ; nmr (DMSO-d_6): δ 10.0 (broad S, 4, exchangeables), 7.52 (S, 1, aromatic H), 7.20 (S, 1, aromatic H), 3.84 (S, 3, methoxy H).

Anal. Calcd. for $C_8H_8N_2O_3S \cdot HCl$: C, 41.29; H, 3.90; N, 12.04. Found: C, 41.40; H, 3.97; N, 11.84.

2-Benzyloxy-1-methoxy-4-nitrobenzene (**9**).

A mixture of 3-hydroxy-4-methoxynitrobenzene (22 g., 0.13 mole) [5-nitroguaiacol (**4**)] and potassium carbonate (21 g., 0.15 mole) in dimethylformamide was heated on a steam bath for 3.0 hours. Benzyl chloride (17 ml., 0.15 mole) was rapidly introduced, and the mixture was heated another 0.5 hour and poured into water (1200 ml.). Recrystallization from 95% ethanol allowed isolation of 24 g. (71%) of product, m.p. 97-98° [lit. m.p. (5) 98° and 93° (two forms)].

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 65.01; H, 5.18; N, 5.34.

2-Amino-5-benzyloxy-6-methoxybenzothiazole Hydrochloride (**11**).

The nitro compound **9** was dissolved in a solution of dimethylformamide (100 ml.) and methanol (200 ml.). Raney nickel No. 28, W. R. Grace & Co. (2 g.) was introduced, and the mixture was reduced on a Parr apparatus in 1.25 hours. Filtration and subsequent concentration of the filtrate to *ca.* 50 ml. was carried out. Addition of water (200 ml.) yielded 18 g. (87%) of amine **10**, m.p. 97-100° [lit. (6) m.p. 100-101°].

To a solution of **10** (15 g., 0.065 mole) and sodium thiocyanate (21 g., 0.26 mole) in methanol (200 ml.) at -10 to -15° was added a solution of methanol (250 ml.) saturated with sodium bromide and containing 3.6 ml. (0.065 mole) of bromine. Addition was carried out over 0.5 hour, and the mixture was stirred overnight without further cooling. The mixture was concentrated to dryness and stirred with water (500 ml.). Dilute ammonium hydroxide (200 ml.) was then added and the resulting solid (16 g.) was collected. The solid was dissolved in hot chloroform (400 ml.), treated with activated charcoal, and filtered. To the filtrate was added 20 ml. of ethanol saturated with hydrogen chloride. The collected precipitate was recrystallized from 2-propanol to give 9.0 g. (43%) of **11**, m.p. 205-206°; ir: ν 6.1μ (C=N); nmr (DMSO-d_6)δ: 9.63 (broad S, 3, exchangeables), 7.63 (S, 1, aromatic H), 7.47 (S, 5, phenyl H), 7.33 (S, 1, aromatic H), 5.17 (S, 2, methylene), 3.83 (S, 3, methoxy).

Anal. Calcd. for $C_{15}H_{14}N_2O_3S \cdot HCl$: C, 55.81; H, 4.68; N, 8.68. Found: C, 55.55; H, 4.73; N, 8.62.

Cleavage of **11** to **4**.

The benzyloxy compound **11** (1.3 g., 0.0040 mole) was refluxed for 2 hours in 3% hydrogen chloride/acetic acid. The cooled mixture was diluted with ether (25 ml.), and the precipitate was collected. Recrystallization from 95% ethanol yielded 0.45 g. (52%) of **4**, m.p. 272-273°. A sample was recrystallized again from 95% ethanol to give m.p. 282-284°. A mixture m.p. with a sample of **4** from the pyranone rearrangement was undepressed. Infrared and nmr spectra matched that of **4**.

Anal. Calcd. for $C_8H_8N_2O_3S \cdot HCl$: C, 41.29; H, 3.90; N, 12.04. Found: C, 41.36; H, 4.08; N, 11.91.

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