

A Synthesis of 4*H*-Thieno[3,2-*c*][1]benzopyran-4-ones by an Application of the Salicylidene-Thiolactone Rearrangement

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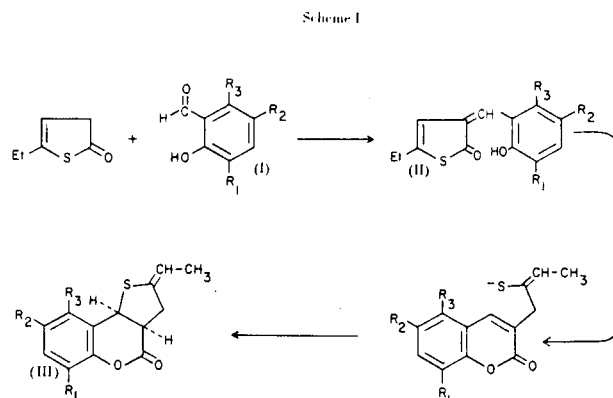
Salicylidenes prepared from 5-ethyl-4-thiolen-2-one undergo base-catalyzed rearrangement (salicylidene-thiolactone rearrangement) to 4*H*-thieno[3,2-*c*][1]benzopyran-4-ones.

J. Heterocyclic Chem., 13, 669 (1976).

Although first prepared in low yield in 1936 by fusion of coumarin with sulfur, the thieno[3,2-*c*]benzopyran system had not been extensively studied until recent pharmacologic studies rekindled interest (1). The bioisosteric thieno[2,3-*c*]benzopyrans and the thieno[3,4-*c*]benzopyrans have been reported to possess analgesic, antipyretic and hallucinogenic activity (2,3). Several patents have also claimed similar potency in the thieno[3,2-*c*]benzopyrans themselves (4,5). In most cases, however, the published syntheses are cumbersome and involve either a highly functionalized thiophene or coumarin as the key intermediate.

The application of our thiolactone rearrangement (6) makes the 4*H*-thieno[3,2-*c*][1]benzopyran-4-ones readily available *via* base catalyzed rearrangement of an isolated salicylidene of 5-ethyl-4-thiolen-2-one (IIa-d). These salicylidenes were prepared in 56-85% yields (see Table I) by the condensation of the appropriate salicylaldehyde and the thiolenone in hydrogen chloride-ethanol medium. All were characterized by positive ferric chloride tests and carbonyl absorptions at $1658 \pm 10 \text{ cm}^{-1}$ in the infrared.

Upon treatment with triethylamine under nitrogen atmosphere, the salicylidenes underwent rearrangement, presumably *via* the intermediacy of a resonance stabilized thiolate anion, to the 4*H*-thieno[3,2-*c*][1]benzopyran-4-ones (IIIa-d) in 25 to 63% yields (see Table I). These products were characterized by the absence of -OH stretch absorptions in the infrared and the presence of a simple lactone carbonyl at $1745 \pm 5 \text{ cm}^{-1}$. Their pmr spectra permitted the assignment of the unsaturation as an exocyclic ethylidene since all products revealed a methyl doublet ($J = 7 \text{ Hz}$) at 1.48 to 1.57 ppm δ and a vinyl proton quartet ($J = 7 \text{ Hz}$) at 5.4 to 5.5 ppm. A methinyl doublet ($J = 6 \text{ Hz}$, *cis*-fusion) was evident at 4.85 to 5.05 ppm corresponding to the benzylic proton at the ring



fusion. Other aliphatic resonances normally appeared as a complex multiplet at 2.7 to 3.7 ppm.

Attempted oxidations of the products (IIIa-d) to the fully aromatized thienobenzopyranones with sulfur, with dichlorodicyanoquinone and with trityl trifluoroacetate were unsuccessful under mild conditions and upon more strenuous conditions yielded tarry mixtures. Dehydrogenations of similar heterocyclics with exocyclic unsaturation have been shown to be much less facile than of those with endocyclic double bonds (7).



EXPERIMENTAL

Infrared spectra were obtained as mineral oil mulls on a Perkin-Elmer 257 spectrophotometer. Pmr spectra were obtained in deuteriochloroform on a Hitachi R-10A nuclear resonance spectrometer and are reported in ppm δ units from TMS. Melting points were obtained in capillaries on a Mel-temp apparatus and are uncorrected. Elemental analyses were provided by Robertson Microanalytical Laboratory, Florham Park, New Jersey.

General Procedure for Preparation of Salicylidenes (IIa-d).

Anhydrous hydrogen chloride gas was bubbled slowly for 5 minutes through a solution of equimolar amounts (15 mmoles) of

Table I

Compound	R ₁	R ₂	R ₃	Formula	% Yield	M.p.	Analysis			
							Caled.		Found	
							C	H	C	H
IIa	H	H	H	C ₁₃ H ₁₂ O ₂ S	80	154-156°	67.23	5.20	66.94	5.38
IIb	H	Cl	H	C ₁₃ H ₁₁ ClO ₂ S	81	164-165°	58.55	4.16	58.50	4.29
IIc	OCH ₃	H	H	C ₁₄ H ₁₄ O ₃ S	56	126-128°	64.11	5.38	63.82	5.48
IIId	H			C ₁₇ H ₁₄ O ₂ S	85	165-167°	72.33	5.00	72.56	5.21
IIIa	H	H	H	C ₁₃ H ₁₂ O ₂ S	55	181-182°	67.23	5.20	66.93	5.39
IIIb	H	Cl	H	C ₁₃ H ₁₁ ClO ₂ S	63	198-199°	58.55	4.16	58.25	4.24
IIIc	OCH ₃	H	H	C ₁₄ H ₁₄ O ₃ S	25	155-156°	64.11	5.38	63.93	5.57
IIId	H			C ₁₇ H ₁₄ O ₂ S	36	210-212°	72.30	5.00	72.37	5.09

5-ethyl-4-thiolen-2-one (8) and the *o*-hydroxyaldehyde (I) in 25 ml. of absolute ethanol. The reaction mixture was held at 0° by an ice-salt bath. The solutions often became intensely yellow and were then agitated at room temperature for 3 hours. If crystals were not already present they were induced by chilling to 0° and scratching with a stirring rod. The yellow-orange product was filtered by suction, washed with a minimum of cold ethanol and recrystallized from ethanol to analytical purity. (See Table I for yields and physical properties).

General Procedure for Rearrangement to the Thieno[3,2-*c*]benzopyran-4-ones (IIIa-d).

A 100 ml. flask was fitted with a condenser, a mercury trap, and a gas inlet. A solution of 3.4 mmoles of II, 25 ml. of chloroform and 0.5 ml. of triethylamine was charged to the flask, flushed with nitrogen, and refluxed under nitrogen atmosphere for 1.5 hours. The solvents were removed *in vacuo* and the residue triturated with cold ethanol to induce crystallization. The solid was collected, washed carefully with 1 to 5 ml. of ethanol and recrystallized from benzene to obtain the analytical material. (See Table I.)

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