(50) H. Fischer and R. Baumler, *Justus Liebigs Ann. Chem.*, **468**, 58 (1929).
(51) A. P. Terent'ev, *J. Gen. Chem. USSR (Engl. Transl.)*, **24**, 1265 (1954).
(52) F. Bohlmann, *Chem. Ber.*, **86**, 657 (1953).
(53) P. S. Skell and G. P. Bean, *J. Am. Chem. Soc.*, **84**, 4655 (1962).
(54) G. P. Bean, *J. Org. Chem.*, **32**, 228 (1967).
(55) J. P. Wibaut and A. R. Gulse, *Proc. K. Ned. Akad. Wet., Ser. B*, **54**, 330 (1951); *Chem. Abstr.*, **47**, 6934*h* (1952).
(56) P. Fournari and J. Tirouflet, *Bull. Soc. Chim. Fr.*, 488 (1963).
(57) H. J. Anderson and S. J. Griffiths, *Can. J. Chem.*, **45**, 2227 (1967).
(58) C. Jaureguiberry, M.-C. Fournie-Zaluski, J.-P. Chevallier, and B. Roques, *C. R. Acad. Sci., Ser. C*, **273**, 276 (1971).
(59) A. P. Terent'ev and L. A. Yanovskaya, *J. Gen. Chem. USSR (Engl. Transl.)*, **21**, 281 (1951).
(60) R. M. Silverstein, E. E. Ryskiewicz, and S. W. Chaikin, *J. Am. Chem. Soc.*, **76**, 4485 (1954).
(61) G. F. Smith, *J. Chem. Soc.*, 3842 (1954).
(62) W. J. King and F. F. Nord, *J. Org. Chem.*, **13**, 638 (1948).
(63) A. W. Weston and R. J. Michaels, *J. Am. Chem. Soc.*, **72**, 1422 (1950).
(64) O. Fischer and E. Hepp, *Chem. Ber.*, **19**, 2251 (1886).
(65) H. Fischer and E. Bartholomaus, *Hoppe-Seyler's Z. Physiol. Chem.*, **76**, 478 (1912); **87**, 257 (1913).
(66) A. J. Birch, *J. Chem. Soc.*, 809 (1945).
(67) G. F. White, *J. Am. Chem. Soc.*, **45**, 779 (1923).
(68) L. P. Fuller, E. Lieber, and Q. B. L. Smith, *J. Am. Chem. Soc.*, **59**, 1150 (1937).
(69) G. A. Cordell, manuscript in preparation.

Thianaphthen-2-one Chemistry. I. Synthesis of 6*H*-Benzothieno[3,2-*c*][1]benzopyran-6-ones (11-Thiacoumestans)

Richard A. Conley and Ned D. Heindel*

Department of Chemistry, Lehigh University, Bethlehem, Pennsylvania 18015

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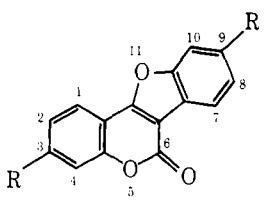
The condensation of thianaphthen-2-one and salicylaldehyde gave 6a,11a-dihydro-6*H*-benzothieno[3,2-*c*][1]benzopyran-6-one (dihydro-11-thiacoumestan). Several analogs were prepared. Oxidation of the dihydro compounds with DDQ (2,3-dichloro-5,6-dicyano-1,4-quinone) gave 6*H*-benzothieno[3,2-*c*][1]benzopyran-6-ones (11-thiacoumestans), a new heterocyclic ring system, and the sulfur analog of the naturally occurring 6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one (coumestan) ring system. The reaction of thianaphthen-2-one with 5-nitrosalicylaldehyde and pyridoxal in alcohol gave the corresponding 2-aryl-2,3-dihydrothianaphthene-3-carboxylates.

Derivatives of the 6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one ring system[1] (commonly called coumestan) have been found in many natural products. 3,9-Dihydroxy-6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one (coumestrol) was isolated from ladino clover and showed marked estrogenic activity.[2,3] The laboratory syntheses of the coumestans have involved multistep reactions.[1,3-5]



R = H, coumestan
R = OH, coumestrol

This paper reports a convenient two-step synthesis of the corresponding sulfur analogs, 6*H*-benzothieno[3,2-*c*][1]benzopyran-6-ones (11-thiacoumestans).[6] The first step involves a unique condensation–rearrangement of thianaphthen-2-one (1) and salicylaldehyde to form 6a,11a-dihydro-6*H*-benzothieno[3,2-*c*][1]benzopyran-6-one (dihydro-11-thiacoumestan, **2a**). Oxidation of the rearrangement product with 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ) gives 6*H*-benzothieno[3,2-*c*][1]benzopyran-6-one (Scheme I).

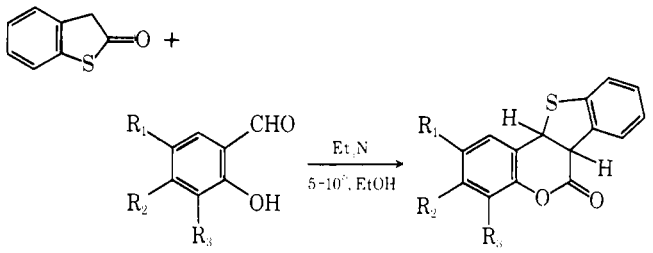
A plausible mechanism for the condensation–rearrangements of thianaphthen-2-one and salicylaldehyde is shown in Scheme I.[7] This suggested pathway has precedent in the mechanism suggested for the Perkin coumarin synthesis.[8] The intermolecular Michael addition of thiophenols to the C-4 position of coumarins is, of course, well known,[9] and an intramolecular addition, proposed herein, is equally likely. Although numerous intramolecular rearrangements of α-salicylidene lactones,[10-14] α-salicylidene oxazolones,[15] and α-salicylidenelactams[16,17] to coumarin derivatives have been reported, this is the first report of such a rearrangement followed by a Michael addition.[18]

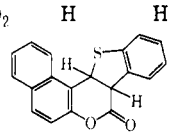
In addition to the parent compound, several substituted dihydrothiacoumestans were prepared (Table I). The dihydro compounds were readily identified by their NMR and ir spectra. The NMR spectra displayed the methinyl protons as characteristic downfield doublets with $J = 7$ Hz (cis methinyls, decoupling collapsing the doublets to singlets). The ir spectra of the dihydrothiacoumestans were characterized by strong carbonyl absorptions at approximately 1755 cm^{-1}.

The 6*H*-benzothieno[3,2-*c*][1]benzopyran-6-one (**4a**) could be obtained by four different synthetic procedures: (1) direct combination of thianaphthen-2-one and salicylaldehyde in refluxing ethanol with triethylamine as a catalyst (10% yield); (2) heating dihydrothiacoumestan with triethylamine (15% yield); (3) sulfur dehydrogenation of dihydrothiacoumestan (73% yield); and (4) DDQ (2,3-dichloro-5,6-dicyano-1,4-quinone) oxidation of dihydrothiacoumestan (75% yield). High yields and simplicity of operation made the DDQ oxidation of the dihydro forms the method of choice for preparation of all thiacoumestans (see Table II).

Wide variations in the relative reactivities observed during the DDQ oxidation of dihydrothiacoumestans to thiacoumestans can be explained by reference to the hydride-abstraction mechanism proposed for DDQ.[19] The dihydrothiacoumestans (**2a–d**) with electron-donating groups were oxidized in good yields by 6–12 hr of reflux. However, the chloro compound **2e** required 59 hr and the naphtho compound **3** required 117 hr for equivalent conversion. Removal by the DDQ of the hydride adjacent to the sulfur would yield a carbonium ion resonance stabilized by both the benzene ring and the sulfur. The more effective stabilization of the benzylic carbonium ion by the electron-donating groups in **2a–d** is reflected in their more rapid oxidation

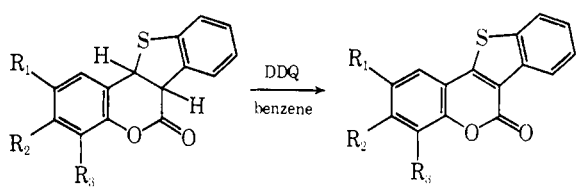
Table I[a]

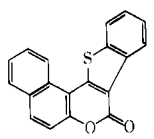


Compd	R_1	R_2	R_3	% yield	Mp, °C	Anal.
2a	H	H	H	79	143.5–145.0	C, H
2b	CH_3O	H	H	80	151.0–153.5	C, H, S
2c	H	OCH_3	H	82	142.0–143.0	C, H, S
2d	H	H	OCH_3	71	173.5–174.5	C, H, S
2e	Cl	H	H	34	226.0–228.0	C, H, S
7[b]	NO_2	H	H	76	198.0–200.0	C, H, S
3				59	215.0–217.0	C, H, S

[a] Satisfactory analytical data (±0.4%) were obtained for the elements indicated. [b] The nitro compound could not be prepared by the general method employed for **2a–e** and **3**. See Experimental Section for this synthesis.

Table II[a]



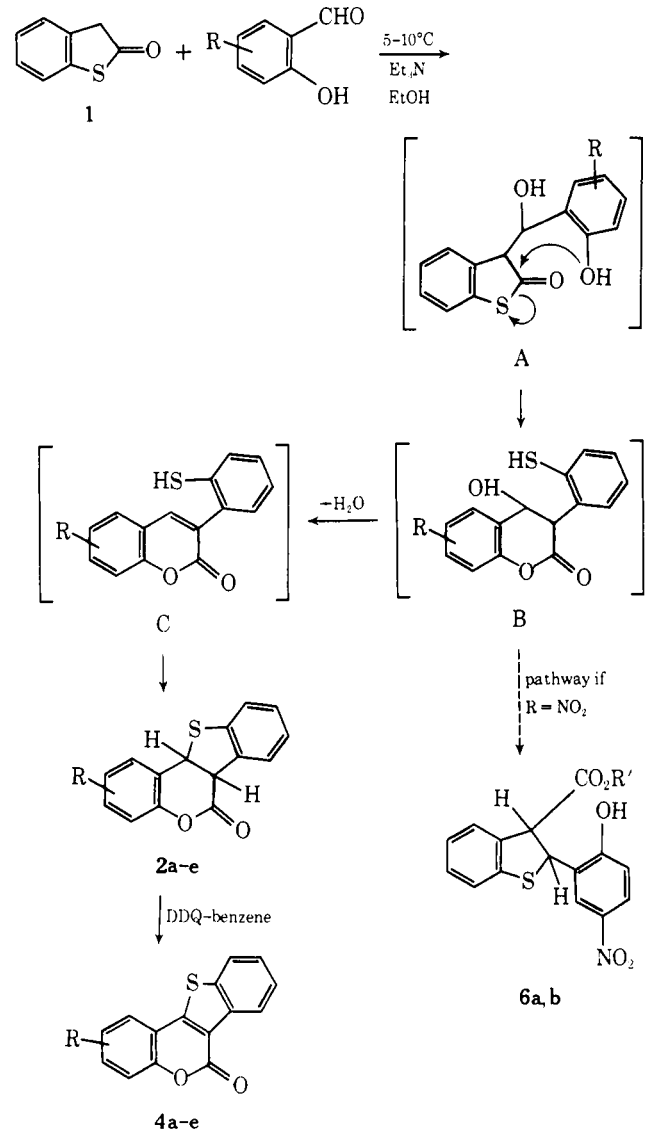
Compd	R_1	R_2	R_3	% yield	Time, hr	Mp, °C
4a	H	H	H	75	11	217.0–217.5
4b	CH_3O	H	H	66	12	187.0–188.0
4c	H	OCH_3	H	66	6	190.0–191.5
4d	H	H	OCH_3	57	10	207.0–208.0
4e	Cl	H	H	57	59	250.5–251.0
8	NO_2	H	H	55	72	261.0–262.0
5				52	117	237.0–239.0

[a] Satisfactory analytical data [±0.4% for C, H, S (N)] were obtained on all compounds listed.

while the longer conversion time required for the oxidation of **2e** is apparently due to destabilization of the transient carbonium ion by the *m*-chloro. The extremely slow rate of reaction of the naphtho compound **3** may be rationalized by the peri hydrogen effect of the proton on carbon 1, hindering the DDQ from abstracting the hydride. After the rate-determining hydride loss, the aromatization is completed by removal of the proton α to the carbonyl.

The thiacoumestans were higher melting and less soluble in common organic solvents than their precursor dihydro forms. This diminished solubility made the obtaining of NMR spectra exceedingly difficult and spectra could be obtained only on **4a** and **4b**. These spectra revealed the absence of the typical cis-coupled methinyl proton pair found in the dihydro compounds. The infrared spectra, however, were of considerable assistance in distinguishing the oxidized from the nonoxidized forms for the α,β unsaturation shifted the carbonyl absorption approximately 40 cm^{-1} toward lower wave numbers.

Scheme I

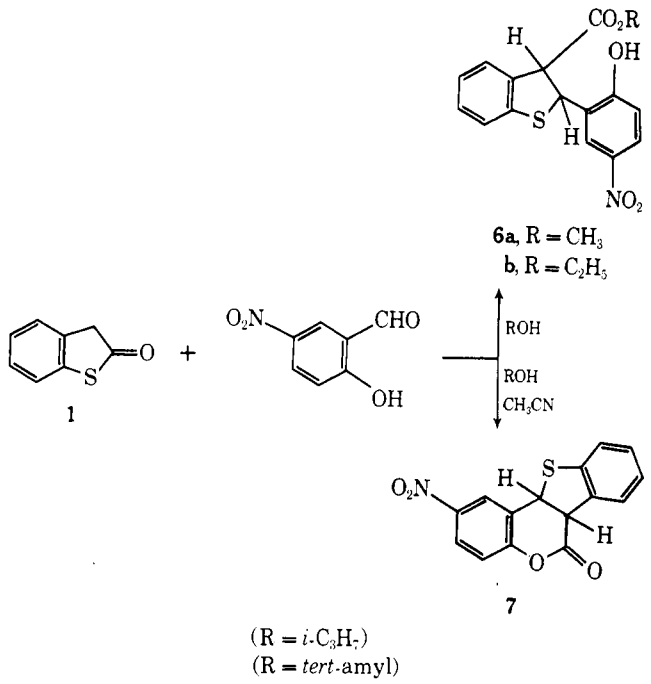


Condensations of Thianaphthen-2-one with 5-Nitrosalicylaldehyde and Pyridoxal. The reaction of **1** and 5-nitrosalicylaldehyde under the normal reaction conditions (ethanol, triethylamine, and cooling in ice) gave ethyl 2-(2-hydroxy-5-nitrophenyl)-2,3-dihydrothianaphthene-3-carboxylate (**6b**) instead of the expected 2-nitrodihydrothiacoumestan (**7**) (see Schemes I and II). Since all other salicylaldehydes studied (vide infra) did not yield the 2-(2-hydroxyphenyl)-2,3-dihydrothianaphthene-3-carboxylates but instead yielded the dihydrothiacoumestans, the result obtained with the 5-nitrosalicylaldehyde is unique. Repeating the reaction with methanol gave the corresponding methyl ester (**6a**) but the use of less nucleophilic solvents such as acetonitrile, *tert*-amyl alcohol, and isopropyl alcohol gave the expected 2-nitrodihydrothiacoumestan (**7**).

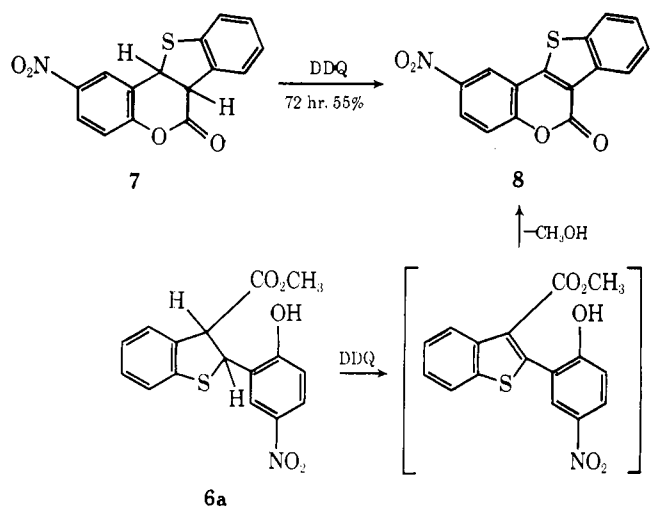
These experimental results implicate a lactone intermediate which is opened by reactive solvents but which proceeds to the 2-nitrodihydrothiacoumestan in less nucleophilic solvents. The fact that 5-nitrosalicylaldehyde is the only salicylaldehyde to undergo this "abnormal reaction" suggests that the nitro group must impart some special properties to this lactone intermediate.

The proposed intermediates A–C and the dihydrothiacoumestan itself (see Scheme I) are all probable species which might be intercepted by methanol or ethanol to produce **6a** or **6b**. No firm experimental evidence establishes

Scheme II



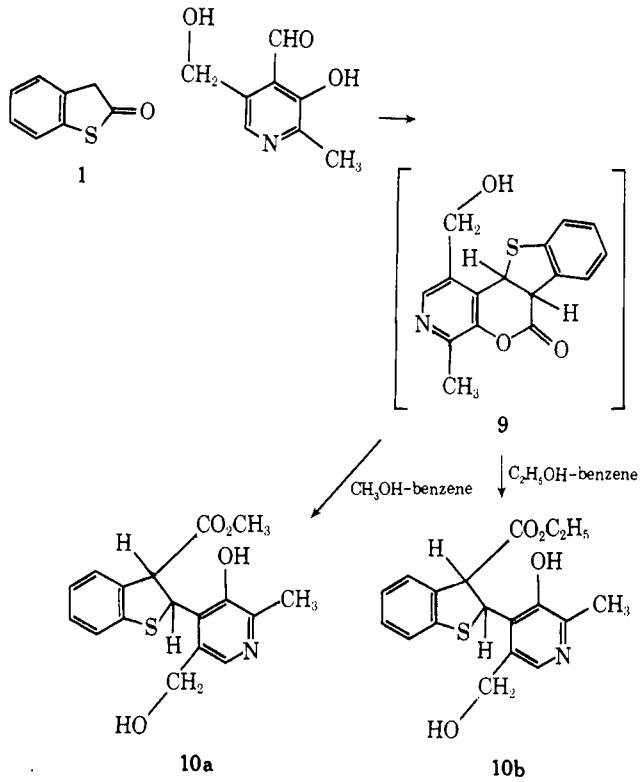
Scheme III



any of these lactones as the precursor of **6a** or **6b** but the authors favor intermediate B. External solvent attack on the thiolactone carbonyl of A as a route to **6a(b)** would not be anticipated to be significantly more likely if R = NO_2 than if R = H. Furthermore, we have found that nitrobenzaldehydes in ethanol form normal benzylidenes without alcoholysis of the thiolactone and an intermediate such as A would be a likely precursor of such benzylidenes. Alcohol attack on the lactone of C would yield a coumarinic ester, a class of compounds known to immediately lactonize to the more stable coumarins.[20] The 2-nitrodihydrothiacoumestan (7) when prepared under other conditions was found to be stable to alcoholysis. Thus while no rigorous proof exists, one strong possibility for formation of **6a,b** is the ethanolysis or methanolysis of B followed by its dehydration and thiol-Michael addition. Furthermore, this intermediate B would explain the unique reaction of the 5-nitrosalicylaldehyde, since the nitro group would be expected to enhance the "leaving group" propensity of the phenolate moiety.

2-Nitrothiacoumestan (8) was synthesized through three different reaction routes: (1) directly from thianaphthen-2-one and 5-nitrosalicylaldehyde, (2) by DDQ oxidation of 2-nitrodihydrothiacoumestan (7), and (3) by DDQ oxidation of the methyl ester **6a**. The oxidation of the methyl ester **6a** to the 2-nitrothiacoumestan 8 was readily predicted from the earlier observations that coumarinate esters (cis cinnamates) immediately lactonize to coumarin.[20] Thus DDQ oxidation of **6a** should yield a labile substituted coumarinate which lactonizes to 8 (Scheme III).

Scheme IV



Thianaphthen-2-one and pyridoxal, upon condensation under the usual reaction conditions with triethylamine catalysis, yielded a crude and labile solid (presumably the pyridopyranone **9**) which upon recrystallization from benzene–methanol gave the methyl ester **10a** and upon recrystallization from benzene–ethanol gave the ethyl ester **10b** (see Scheme IV). The excellent "leaving group" propensity of the 3-hydroxypyridine makes this situation the parallel of the *p*-nitrophenol case previously discussed. Attempts to isolate the presumed intermediate 6*H*-benzothieno[3,2-*c*]pyrido[4,3-*e*]pyran-6-one (**9**) were unsuccessful.

Experimental Section

General. Infrared spectra were recorded on a Beckman IR-33 spectrophotometer as Nujol mulls or in solution using 0.1-mm sodium chloride liquid cells. NMR spectra were obtained on a Hitachi Perkin-Elmer R-20A spectrometer with tetramethylsilane as the internal standard. Mass spectra were recorded at the University of Delaware, Newark, Del., on a CED Model 21-110B double focusing spectrometer. Microanalyses were performed by Dr. G. I. Robertson, Jr., Florham Park, N.J. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

General Procedure for the Preparation of 6a,11a-Dihydro-6*H*-benzothieno[3,2-*c*][1]benzopyran-6-ones (Dihydro-11-thiacoumestans)(2a–e, 3). Equimolar quantities (6.6 mmol) of thianaphthen-2-one (1)[21,22] and the appropriate salicylaldehyde were dissolved or slurried in absolute ethanol (2–6 ml) and cooled with stirring in an ice bath. After the mixture was stirred in the cold for 30 min, 4–5 drops of triethylamine was added and product began to precipitate after an additional 15–30 min. After stirring for several hours in the cold, petroleum ether (bp 60–110°) was added, and the crude product was filtered and washed several times with

cold petroleum ether. The product was recrystallized from benzene–petroleum ether to analytical purity (see Table I).

The characteristic spectral feature of **2a–e** is the coupled methinyl set at δ 4.35 ± 0.02 and 5.14 ± 0.04 ppm (in $CDCl_3$). Compound **2c** was examined in Me_2SO-d_6 owing to insufficient solubility in $CDCl_3$ and the same proton set was observed, δ 4.73 (CHCO) and 5.47 (CHS). The carbonyl absorptions are found at 1760 ± 5 cm^{-1} ($CHCl_3$) for **2a–e** and **3**.

6*H*-Benzothieno[3,2-*c*][1]benzopyran-6-one (4a). Four methods were employed for the synthesis of this substance; the last (oxidation of the dihydro precursors with DDQ) became the general method for synthesis for all analogs of the class (see Table II).

A. Direct Preparation from 1 and Salicylaldehyde. Equimolar quantities (6.6 mmol) of **1** and salicylaldehyde were dissolved in 3 ml of Et_3N and 1 ml of MeOH and the mixture was refluxed for 0.5 hr. Evaporation of the solvents gave a red semisolid which when triturated with boiling MeOH yielded 0.25 g (15%) of **4a**: mp 216.0–217.0°; NMR ($CDCl_3$) δ 6.90–8.80 (m, ArH); ir ($CHCl_3$) 1720 cm^{-1} (C=O); mass spectrum m/e 252 (P).

B. Sulfur Dehydrogenation of 2a. A mixture of 0.25 g (0.98 mmol) of **2a** and 0.06 g (1.96 mmol) of sulfur was fused (H_2S was evolved) in an oil bath at 215°. The melt, after 15 min of heating, solidified and the crude product was dissolved in hot benzene and filtered. Cooling the solution returned 0.18 g (75%) of tan powder (**4a**), mp 215.0–217.0°, mmp 215.0–217.0° (no depression).

C. Refluxing 2a with Triethylamine. A slurry of 0.50 g (1.96 mmol) of **2a**, 8 ml of absolute EtOH, and 8 drops of Et_3N was heated at reflux for 2 hr. Evaporation yielded an oil which when triturated with boiling MeOH gave 0.05 g (10%) of solid (**4a**): mp 213.0–215.0°; identical infrared spectrum with that of previously prepared material.

D. DDQ Oxidation. General Procedure for the Preparation of 6*H*-Benzothieno[3,2-*c*][1]benzopyran-6-ones (11-Thiacoumestans) (4a–e and 5). Equimolar quantities of the 6a,11a-dihydro-6*H*-benzothieno[3,2-*c*][1]benzopyran-6-one (**2a–e** and **3**) and DDQ in 20 ml of sodium-dried benzene were refluxed for the times stated in Table II. The initially dark black solution became brown during the reaction with the precipitation of the brown hydroquinone. The hydroquinone was removed by hot filtration through a sintered glass funnel and was then washed with hot benzene to ensure complete extraction of the product. The filtrate was partially evaporated and ether was added to precipitate the oxidized product. Upon cooling, crystals precipitated and these were filtered and washed several times with cold ether. One recrystallization from benzene–ether gave the analytical sample (see Table II for data).

Methyl 2-(2-Hydroxy-5-nitrophenyl)-2,3-dihydrothianaphthene-3-carboxylate (6a). A slurry of 1.00 g (6.6 mmol) of **1** and 1.10 g (6.6 mmol) of 5-nitrosalicylaldehyde in 10 ml of MeOH was cooled to 0°, 5 drops of Et_3N was added, and after 2.5 hr of stirring a solid began to precipitate. After an additional 4 hr, petroleum ether was added and the mixture was filtered to isolate 1.00 g (46%) of white crystals of **6a**: mp 153.0–155.0°C (twice, benzene–petroleum ether); NMR (Me_2SO-d_6) δ 3.30 (s, 3 H, OCH_3), 4.80 (d, 1 H, J = 8 Hz, $CHCOOCH_3$), 5.65 (d, 1 H, J = 8 Hz, SCH), 6.80–8.12 (m, 8 H, ArH and OH); ir (Nujol) 3340 (OH) and 1710 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{13}NO_5S$: C, 58.00; H, 3.95; N, 4.23; S, 9.68. Found: C, 58.08; H, 4.18; N, 4.03; S, 9.38.

Ethyl 2-(2-Hydroxy-5-nitrophenyl)-2,3-dihydrothianaphthene-3-carboxylate (6b). A slurry of 1.00 g (6.6 mmol) of **1** and 1.10 g (6.6 mmol) of 5-nitrosalicylaldehyde in 10 ml of absolute EtOH was cooled in an ice bath, 5 drops of Et_3N was added, and the slurry was stirred for 3 hr. Petroleum ether was added and the reaction mixture was filtered to yield 1.65 g of a crude product, mp 140–156°. Recrystallization from benzene–ethanol gave 1.17 g (51%) of **6b**, white, fluffy powder: mp 177.0–179.0°; NMR (Me_2SO-d_6) δ 0.82 (t, 3 H, J = 7 Hz, OCH_2CH_3), 3.80 (q, 2 H, J = 7 Hz, OCH_2CH_3), 4.87 (d, 1 H, J = 8 Hz, $CHCO_2C_2H_5$), 5.70 (d, 1 H, J = 8 Hz, SCH–), 6.80–7.60 (m, 5 H, ArH), 7.90–8.20 (m, 2 H, ArH), 10.50–11.40 (br, 1 H, OH, D_2O exchangeable); ir (Nujol) 3320 (OH) and 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{17}H_{15}NO_5S$: C, 59.12; H, 4.38; N, 4.06. Found: C, 59.22; H, 4.55; N, 4.10.

2-Nitro-6a,11a-dihydro-6*H*-benzothieno[3,2-*c*][1]benzopyran-6-one (7). A. Acetonitrile Reaction. A slurry of 1.00 g (6.6 mmol) of **1** and 1.10 g (6.6 mmol) of 5-nitrosalicylaldehyde in 5 ml of acetonitrile was cooled in an ice bath for 0.5 hr, 5 drops of Et_3N was added, and a solid began precipitating. After an additional 5 hr of stirring in the cold, the mixture was filtered to isolate 1.50 g (76%) of crude white solid with a melting range of 188–192°. Recrystallizations from acetonitrile gave 0.40 g (20%) of **7** as white granules: mp 198–200°; ir (Nujol) 1760 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 4.92 (d, 1 H, J = 7.5 Hz, CHCO), 5.72 (d, 1 H, J = 7.5 Hz, CHS), and 7.0–7.7 (m, ArH).

Anal. Calcd for $C_{15}H_9NO_4S$: C, 60.19; H, 3.03; N, 4.68; S, 10.71. Found: C, 60.04; H, 3.25; N, 4.79; S, 10.99.

B. *tert*-Amyl Alcohol Reaction. A slurry of 6.6 mmol each of **1** and 5-nitrosalicylaldehyde in 5 ml of *tert*-amyl alcohol was chilled in an ice water bath, 3 drops of Et_3N was added, and the mixture was agitated in the cold for 7 hr. The product was filtered, washed with cold petroleum ether (bp 30–60°), and dried to yield 1.80 g (91%) of **7**, which, although of broad and low melting point (mp 160–167°), possessed an ir spectrum identical with that of the analytical sample. Two recrystallizations (acetonitrile) raised the melting point to 186–190°. A repeat of the experiment in 2-propanol as solvent gave similar results, an 86% yield crude **7** (mp 168–175°) whose melting point was raised to 190–193° after two recrystallizations from acetonitrile.

Anal. Calcd for $C_{15}H_9NO_4S$: C, 60.19; H, 3.03; N, 4.68; S, 10.71. Found: C, 60.04; H, 3.25; N, 4.79; S, 10.99.

2-Nitro-6*H*-benzothieno[3,2-*c*][1]benzopyran-6-one (8). A. Directly from Thianaphthen-2-one and 5-Nitrosalicylaldehyde. An orange-yellow solution of 6.6 mmol each of **1** and 5-nitrosalicylaldehyde was cooled in an ice bath, 10 drops of Et_3N was added, and precipitation of product ensued within 10 min. The reaction mixture was stirred at 15° for 6 hr, petroleum ether (bp 30–60°) was added, and the solution was stirred at 35° for 5 hr. Filtration and air drying gave 0.25 g (13%) of the 2-nitrothiacoumestan (**8**) as a tan solid, mp 256–260°, ir ($CHCl_3$) 1725 cm^{-1}. Recrystallization from benzene yielded the analytical sample, mp 261–262°.

Anal. Calcd for $C_{15}H_7NO_4S$: C, 60.60; H, 2.37; N, 4.71; S, 10.78. Found: C, 60.68; H, 2.68; N, 4.56; S, 10.57.

B. DDQ Oxidation of the Methyl Ester 6a. A solution of 0.15 g (0.5 mmol) of the methyl ester **6a** and 0.13 g (0.6 mmol) of DDQ in 20 ml of sodium-dried benzene was refluxed for 72 hr and filtered hot to remove the precipitated hydroquinone. The filtrate was partially evaporated and the fluffy 2-nitrothiacoumestan (**8**) precipitated. Ether (25 ml) was added, the filtrate was chilled, and the fluffy white solid (0.13 g, 97%) was removed, mp 258–260°. Recrystallization from benzene raised the melting point to 263.0–265.0°, mmp 263.5–264.5° (undepressed).

C. DDQ Oxidation of 7 to 8. Following the general procedure previously outlined for DDQ preparation of **4a–e** and **5**, compound **8** (mp 263–265° from benzene) was prepared in 55% yield by oxidation of **7** (see Table II).

Methyl 2-(3-Hydroxy-5-hydroxymethyl-2-methyl-4-pyridyl)-2,3-dihydrothianaphthene-3-carboxylate (10a). A slurry of equimolar amounts (6.6 mmol) of **1** and pyridoxal hydrochloride in 6 ml of absolute EtOH was cooled to 10°, 5 drops of Et_3N was added, and the medium was stirred for 1 hr. This mixture was then dissolved in water, solid $NaHCO_3$ was added until slight alkalinity was achieved, and the precipitate was filtered, washed with petroleum ether (bp 30–60°), and air dried to give 1.46 g of crude light yellow solid (presumably the lactone **9**: mp 98–106° (unclear melt); NMR (Me_2SO-d_6) δ 2.47 (s, 3 H, pyr-CH_3), 4.67 (s, 2 H, pyr-CH_2OH), 4.80 (d, 1 H, J = 7 Hz, –CHCO), 5.18–5.80 (broad, 1 H, CH_2OH), 5.68 (d, 1 H, J = 7 Hz, CHS), 7.00–7.70 (m, 4 H, ArH), 8.20 (s, 1 H, pyr-H). Recrystallization from 20 ml of 50:50 benzene–MeOH yielded 1.43 g (66%) of the methyl ester as an off-white powder: mp 182.0–185.0° dec; NMR (Me_2SO-d_6) δ 2.43 (s, 3 H, pyr-CH_3), 3.75 (s, 3 H, OCH_3), 4.58 (s 2 H, pyr-CH_2OH), 4.83–5.83 (broad, 1 H, CH_2OH, D_2O exchangeable), 5.12 (d, 1 H, J = 8 Hz, CHS), 7.00–7.50 (m, 4 H, ArH), 7.98 (s, 1 H, pyr-H), D_2O showed two exchangeable protons; ir (Nujol) 3150 (OH) and 1730 cm^{-1} (C=O). An analytical sample of **10a** was prepared by recrystallization from alcohol, mp 191.5–193.0° dec.

Anal. Calcd for $C_{17}H_{17}NO_4S$: C, 61.62; H, 5.17; N, 4.23; S, 9.68. Found: C, 61.37; H, 5.45; N, 4.04; S, 9.51.

Ethyl 2-(3-Hydroxy-5-hydroxymethyl-2-methyl-4-pyridyl)-2,3-dihydrothianaphthene-3-carboxylate (10b). Following the exact procedure outlined for **10a**, the crude, labile presumed lactone **9** was again isolated and when recrystallized from benzene–EtOH gave 0.51 g of white, fluffy solid **10b**: mp 171.5–173.0° dec; NMR (Me_2SO-d_6) δ 1.20 (s, 3 H, J = 7 Hz, OCH_2CH_3), 2.40 (s, 3 H, pyr-CH_3), 4.17 (q, 2 H, J = 7 Hz, OCH_2CH_3), 4.58 (s, 2 H, pyr-CH_2OH), 4.80–5.70 (broad, 1 H, D_2O exchangeable, pyr-CH_2OH), 5.05 (d, 1 H, J = 8 Hz, –CHCO), 5.95 (d, 1 H, J = 8 Hz, –CHS),

7.00–7.40 (m, 4 H, ArH), 7.95 (s, 1 H, pyr-H), D_2O showed two exchangeable protons; ir (Nujol) 3120 (OH) and 1730 cm^{-1} (C=O). A second recrystallization from benzene–EtOH gave 0.35 g of white analytically pure solid **10b**, mp 172.0–173.0° dec.

Anal. Calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06; S, 9.28. Found: C, 62.75; H, 5.62; N, 3.82; S, 9.51.

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Registry No.—**1**, 496-31-1; **2a**, 54711-32-9; **2b**, 54711-33-0; **2c**, 54711-34-1; **2d**, 56404-07-0; **2e**, 56404-08-1; **3**, 56404-09-2; **4a**, 54711-35-2; **4b**, 54711-36-3; **4c**, 54711-37-4; **4d**, 56404-10-5; **4e**, 56404-11-6; **5**, 56404-12-7; **6a**, 56404-13-8; **6b**, 56404-14-9; **7**, 56404-15-0; **8**, 56404-16-1; **9**, 56404-17-2; **10a**, 56404-18-3; **10b**, 56404-19-4; salicylaldehyde, 90-02-8; 5-methoxysalicylaldehyde, 672-13-9; 4-methoxysalicylaldehyde, 673-22-3; 3-methoxysalicylaldehyde, 148-53-8; 5-chlorosalicylaldehyde, 635-93-8; 5-nitrosalicylaldehyde, 97-51-8; sulfur, 7704-34-9; triethylamine, 121-44-8; DDQ, 84-58-2; MeOH, 67-56-1; EtOH, 64-17-5; acetonitrile, 75-05-8; *tert*-amyl alcohol, 75-85-4; pyridoxal HCl, 65-22-5.

References and Notes

(1) Two excellent reviews on coumestan chemistry: (a) F. M. Dean, "The Total Synthesis of Naturally Occurring Oxygen Ring Compounds", in "The Total Synthesis of Natural Products", Vol. 1, J. ApSimon, Ed., Wiley, New York, N.Y., 1973; (b) A. Mustafa, "Furopyrans and Furopyrones", in "The Chemistry of Heterocyclic Compounds", Vol. 23, A. Weissberger, Ed., Wiley, New York, N.Y., 1967.
(2) R. A. Michell, A. N. Booth, A. L. Livingston, and E. M. Bickoff, *J. Med. Pharm. Chem.*, **5**, 321 (1962).
(3) O. H. Emerson and E. M. Bickoff, *J. Am. Chem. Soc.*, **80**, 4381 (1958).
(4) H. W. Wanslick, R. Gritsky, and H. H. Heidepriem, *Chem. Ber.*, **96**, 305 (1963).
(5) L. Jurd, *J. Org. Chem.*, **29**, 3036 (1964).
(6) Preliminary report: R. A. Conley and N. D. Heindel, *Chem. Commun.*, 773 (1974).
(7) Alternatively a salicylidene intermediate could be formed and undergo the rearrangement. A problem with this mechanism is that the trans isomer (thermodynamically stable) would be formed and a trans to cis isomerization would be required for rearrangement. Zimmer, however, has rearranged 3-(salicylidene)benzofuran-2-ones to 3-(2-hydroxyphenyl)coumarins by refluxing in triethylamine (ref 12).
(8) J. A. Joule and G. F. Smith, "Heterocyclic Chemistry", Van Nostrand-Reinhold, Princeton, N.J., 1972, Chapter 14.
(9) A. Mustafa, M. Kamel, M. A. Allam, A. Harhash, and A. Hassan, *J. Am. Chem. Soc.*, **78**, 5011 (1956).
(10) D. H. Marrian and P. B. Russell, *J. Chem. Soc.*, 753 (1946).
(11) R. Walter and H. Zimmer, *J. Heterocycl. Chem.*, **1**, 217 (1964).
(12) R. Walter, H. Zimmer, and T. C. Purcell, *J. Org. Chem.*, **31**, 3854 (1966).
(13) R. Walter, D. Theodoropoulous, and T. C. Purcell, *J. Org. Chem.*, **32**, 1649 (1967).
(14) H. Zimmer et al., *Tetrahedron Lett.*, 5435 (1968).
(15) R. Walter, T. C. Purcell, and H. Zimmer, *J. Heterocycl. Chem.*, **3**, 235 (1966).
(16) H. Zimmer, D. C. Armbruster, S. P. Kharidia, and D. C. Lankin, *Tetrahedron Lett.*, 4053 (1969).
(17) R. G. Gailey and H. Zimmer, *Tetrahedron Lett.*, 2839 (1970).
(18) Zimmer (ref 14) has reported that the rearrangement of α-salicylidene-γ-thiobutyrolactone gave 3-(2-mercaptoethyl)coumarin and not a Michael addition product.
(19) L. M. Jackman, *Adv. Org. Chem.*, **2**, 1 (1960).
(20) J. L. Abernethy, *J. Chem. Educ.*, **46**, 561 (1969).
(21) R. P. Dickinson and B. Iddon, *J. Chem. Soc. C*, 1926 (1970).
(22) W. C. Lumma, Jr., G. A. Dutra, and C. A. Voeker, *J. Org. Chem.*, **35**, 3442 (1970).

Darzens Synthesis of Glycidic Thiol Esters. Formation of a β-Lactone By-product[1]

Dineshkumar J. Dagli, Ping-Shun Yu, and James Wemple*

Department of Chemistry, University of Detroit, Detroit, Michigan 48221

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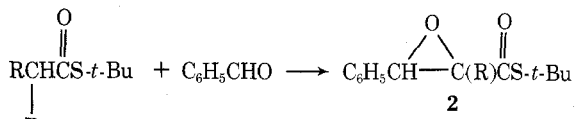
The Darzens condensation has been used in the preparation of glycidic thiol esters. Aliphatic ketones and aromatic and aliphatic aldehydes may be used as substrates. *S*-Benzyl and *S*-*tert*-butyl thiolglycidates were prepared. In general 2-bromothiol esters gave higher yields than the corresponding 2-chlorothiol esters. The low yields obtained with 2-chlorothiol esters are due in part to competing formation of an α-chloro-β-lactone by-product. Results have been obtained that suggest that a carbene intermediate is not involved in the Darzens synthesis of glycidic thiol esters.

A great deal of attention has been given to preparative and mechanistic aspects of the Darzens synthesis of glycidic (oxygen) esters.[2] Recently[1b] we have found that it is also possible to carry out a Darzens synthesis of glycidic thiol esters (**2**). In the formation of the glycidic thiol esters it is important to use nonnucleophilic bases such as sodium hydride or lithium bis(trimethylsilyl)amide and relatively polar aprotic solvents including tetrahydrofuran and dimethylformamide. We have also found that α-bromothiol ester reactants are preferable in most cases to the corresponding α-chlorothiol esters.[1b]



1a, R = H
b, R = CH_3

When these facts are kept in mind the Darzens reaction provides the best available method for the synthesis of S-aliphatic glycidic thiol esters.[3] In this report we would like to comment on the generality of this reaction and also certain mechanistic aspects of the process. At the outset it should be pointed out that even when working within the previously described limits[1b] the proper choice of reaction conditions is critical in obtaining a successful reaction. This situation may be contrasted with the wide variety of conditions successfully employed in the normal Darzens glycidic ester condensation.[2] It is important to understand something about these limitations in order to take full advantage of the Darzens reaction in the synthesis of glycidic thiol esters.

Results and Discussion

In this discussion it will be useful to make reference to the currently accepted mechanism[2b,c,d,h,i,l] for the Darzens reaction (Scheme I). Although we have not carried out an extensive examination of the mechanism of the Darzens synthesis of glycidic thiol esters, we have checked certain points to see if major differences are apparent. It has been argued earlier from a study of the reaction of ethyl 2-chlo-