Table I. Yields and Physical Properties of Substituted *O*- and *S*-(2-Methoxyphenyl) *N,N*-Dimethylthiocarbamates and 2*H*-1,3-Benzoxathiol-2-ones[a]

			anal.					
			% calcd			% found		
compd	mp, °C	yield, %	C	H	N	C	H	N
		O-(2-Methoxyphenyl) *N,N*-Dimethylthiocarbamates						
1a	52-56[b]	42						
1b	86-88	49	58.65	6.71	6.22	58.57	6.61	6.14
1c	58-60	42	48.89	4.89	5.70	48.97	4.88	5.72
1d	66-68	51	54.75	6.27	5.81	55.09	6.41	5.96
1e	144-146	39	54.75	6.27	5.81	54.86	6.46	5.77
		S-(2-Methoxyphenyl) *N,N*-Dimethylthiocarbamates						
2a	89-91[c]	72[d]						
2b	67-69	56[d,e]	58.65	6.71	6.22	58.70	6.84	6.18
2c	104-106	21[f]	48.89	4.89	5.70	48.88	4.91	5.73
2d	84-86	55[f,e]	54.75	6.27	5.81	54.89	6.38	5.88
2e	122-127	75[d]	54.75	6.27	5.81	54.62	6.38	5.73
		2*H*-1,3-Benzoxathiol-2-ones						
3a	[g]	88						
3b	71-73	100	57.81	3.64		57.70	3.76	
3c	87-89	81	45.04	1.62		45.28	1.77	
3d	142-144	87	50.00	2.40		50.10	2.39	
3e	83-85[h]	44	52.74	3.32		52.82	3.28	
3f	155-157[h]	67	50.00	2.40		50.25	2.60	

[a] Satisfactory analytical data (±0.4% for C, H, N on **1b-e** and **2b-e**; ±0.3% for C, H on **3b-f**) were reported. [b] Lit.[6] mp 61-62 °C. [c] Lit.[6] mp 93-95 °C. [d] Rearrangement *T*, 280 °C. [e] Rearrangement in sulfolane. [f] Rearrangement *T*, 260 °C. [g] Bp 85-90 °C (0.4 mm) [Lit.[9] bp 72 °C (0.25 mm)]. [h] Obtained from **2e**; see Discussion and Experimental Sections.

oil which crystallized to sticky yellow crystals which were shown by TLC to contain two components, one of which was identified by comparison with resorcinol. Recrystallization from diisopropyl ether gave colorless needles, mp 80–82 °C. Sublimation at 65 °C (5 μm) gave an analytical sample; mp 83–85 °C (see Table I); IR (Nujol) 1750, 755, 700 cm^{-1}.

4-Hydroxy-2*H*-1,3-benzoxathiol-2-one (3f). To a melt of 16 g of pyridine hydrochloride at 200 °C under N_2 was added 5.5 g (22.7 mmol) of **2e**, and the yellow-brown solution was magnetically stirred at 200 °C for 1.25 h, cooled to 25 °C, and added to 30 mL of water. The mixture was extracted with ether, which was washed with water, dried superficially with phase separation paper, and concentrated on a rotary evaporator to give 3.0 g (78.8%) of solid, mp 136–152 °C, which was recrystallized from benzene to give mp 155–157 °C (see Table I): IR (Nujol) 3250, 1700, 760, 700 cm^{-1}.

6-Methoxy-2*H*-1,3-benzoxathiol-2-one. The sodium salt was prepared by treating 6.35 g (0.037 mol) of 6-hydroxy-2*H*-1,3-benzoxathiol-2-one (from resorcinol and CuSCN[18]) in 30 mL of ethylene glycol–dimethyl ether (dried with 4A molecular sieves) with 0.89 g (0.037 mol) of NaH under N_2 at 20 °C. To a yellow suspension was then added 5.25 g (0.037 mol) of MeI in 10 mL of ethylene glycol–dimethyl ether at 10 °C, and the cloudy solution was stirred overnight at 25 °C. The reaction mixture was added to 75 mL of ice water containing 0.5 mL of concentrated HCl to give a yellow-brown semisolid, which was extracted with ether, washed with water, dried with phase separation paper, and concentrated on a rotary evaporator to give a yellow-brown oil which partly solidified. The product was recrystallized from methanol to give yellow crystals, mp 57–59 °C [3.40 g (50.5%)]. Recrystallization from diisopropyl ether gave white crystals: mp 61–62 °C (lit. mp 62–64 °C,[21] 61–62 °C[22]); IR (Nujol) 1725, 860, 780 cm^{-1}.

Anal. Calcd for $C_8H_6O_3S$: C, 52.74; H, 3.32. Found: C, 52.78; H, 3.34.

2-Mercaptoresorcinol. To a nitrogen-blanketed slurry of 0.5 g (3 mmol) of 4-hydroxy-2*H*-1,3-benzoxathiol-2-one (**3f**) in an equal volume of water was added 5.1 mL of 2 N NaOH. The mixture was stirred without heating (exotherm to ca. 30 °C) for 20 min and acidified with concentrated HCl with ice bath cooling to pH ca. 3. The resulting suspension was extracted with ether, and the ether layer was washed once with a small volume of water, dried with phase separation paper, and concentrated on a rotary evaporator at 60 °C to give a yellow oil (0.40 g, 95%) which partly solidified. The product was purified by sublimation at 60 °C (8 μm) to give the following: mp 75–78 °C; IR (Nujol) 3380, 2500, 770, 695 cm^{-1}.

Anal. Calcd for $C_6H_6O_2S$: C, 50.68; H, 4.26. Found: C, 50.74; H, 4.32.

After 10 days at 25 °C, this material had mp 70–127 °C.

4-Mercaptoresorcinol. The hydrolysis of 2.5 g (14.9 mmol) of 6-hydroxy-2*H*-1,3-benzoxathiol-2-one (mp 154–156 °C, from resorcinol and CuSCN) in 25 mL of 2 N NaOH was carried out as described above for 2-mercaptoresorcinol to give 1.95 g (94%) of yellow oil which solidified: mp 106–110 °C. Sublimation at 60 °C (5 μm) gave white crystals: mp 109–111 °C (lit.[19] mp 110–111 °C); IR (Nujol) 3380, 2495, 900, 835, 795, 690 cm^{-1}.

Anal. Calcd for $C_6H_6O_2S$: C, 50.68; H, 4.26. Found: C, 50.55; H, 4.21.

After 10 days at 25 °C, this material had mp 106–110 °C.

Registry No. **1a**, 13522-62-8; **1b**, 71912-75-9; **1c**, 71912-76-0; **1d**, 71912-77-1; **1e**, 71912-78-2; **2a**, 13511-97-2; **2b**, 71912-79-3; **2c**, 71912-80-6; **2d**, 71912-81-7; **2e**, 71912-82-8; **3a**, 7735-53-7; **3b**, 71912-83-9; **3c**, 71912-84-0; **3d**, 71912-85-1; **3e**, 71912-86-2; **3f**, 95-18-1; 4-chloro-2-methoxyphenol, 16766-30-6; guaiacol, 90-05-1; 6-methoxy-2*H*-1,3-benzoxathiol-2-one, 6074-48-2; 6-hydroxy-2*H*-1,3-benzoxathiol-2-one sodium salt, 71912-87-3; 6-hydroxy-2*H*-1,3-benzoxathiol-2-one, 4991-65-5; 2-mercaptoresorcinol, 2103-60-8; 4-mercaptoresorcinol, 2553-70-0; sodium 2-methoxyphenoxide, 13052-77-2; sodium 2-methoxy-4-methylphenoxide, 71912-88-4; sodium 2-methoxy-4-chlorophenoxide, 71912-89-5; sodium 2,4-dimethoxyphenoxide, 35471-47-7; sodium 2,6-dimethoxyphenoxide, 71912-90-8; *N,N*-dimethylthiocarbamoyl chloride, 16420-13-6.

Regiospecific 2β-Chloro-3-tropinone Preparation. A Synthesis of Tropinone and Pseudopelletierine

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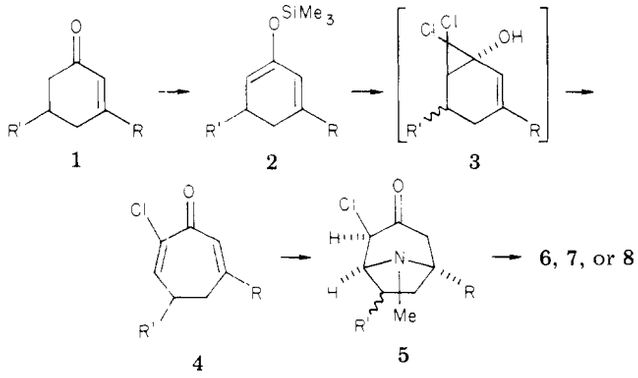
Recent synthetic work on tropane alkaloids has focused on schemes which allow specific and diverse tropane structural modification.[2-4] We now report a route to the

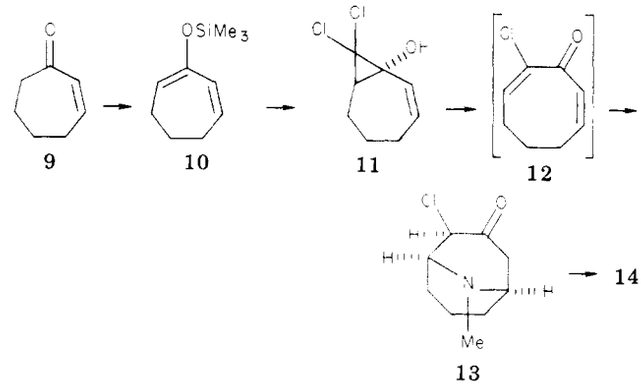
(1) Stephen Harris Cook Memorial Scholar.

0022-3263/79/1944-4973$01.00/0

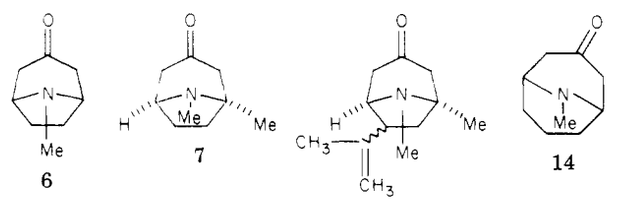
Scheme I



Scheme II



3-tropinone system which employs bisconjugate addition of a primary amine to a regiospecifically generated 2-chloro-2,6-cycloheptadienone.[5,6] The conjugate addition product, a specific 2β-chloro-3-tropinone, can be further elaborated or reduced to the parent tropinone. The scheme utilizes 2-cyclohexenones as the starting points for 2β-chloro-2,6-cycloheptadienones, making available a broad range of skeletal and functional features on the precursor 2,6-cycloheptadienone and resultant 3-tropinone. Central to the sequence is the regiospecific dichlorocyclopropanation of dienylsilyl ethers[7] to generate α,α-dichlorocyclopropanoid intermediates. We illustrate the use of this scheme by preparation of 3-tropinone (**6**) and two analogue tropinones (**7** and **8**) from their 2-cyclohexenone precursors and of pseudopelletierine (**14**) from 2-cycloheptenone (**9**).



The ultimate tropane regiochemistry and skeletal features are established at the outset of the sequence by generation of dienylsilyl ether **2** from the requisite cyclohexenone substrate **1** (Scheme I). Dichlorocarbene addition and hydrolysis gave the intermediate α,α-dichlorocyclopropanol **3**[5] which can be isolated or can rearrange to the α-chlorodienone **4**. For the synthesis of tropinone **6** (Scheme I), 2-cyclohexenone (**1**) (R = R′ = H) was converted into 2-[(trimethylsilyl)oxy]-1,3-cyclohexadiene (**2**) (R = R′ = H) as described by Rubottom and Gruber[7] (80%). Dichlorocyclopropanation of diene **2** followed by acid-catalyzed hydrolysis gave 2-chloro-2,6-cycloheptadienone (**4**) (R = R′ = H) directly (73%). Addition of cold methanolic methylamine afforded chlorotropinone (**5**) (R = R′ = H). Only 2β-chloro-3-tropinone (**5**) could be isolated after workup, despite spectral evidence that both 2-chlorotropinone epimers are formed kinetically in this reaction.[8] The synthesis of tropinone **6** (R = R′ = H) was completed by reduction of **5** with tributyltin hydride (70%). In similar fashion and without chromatographic purification of intermediates, 3-methyl-2-cyclohexenone (**1**) (R = Me; R′ = H) was converted into 1-methyl-3-tropinone (**7**) in 22% yield, and carvone (**1**) (R = Me; R′ = isopropenyl) was transformed into a separable epimeric mixture [75% (6α-isopropenyl):25% (6β-isopropenyl)] of 3-tropinone analogues **8** in 18% yield.

For the synthesis of pseudopelletierine (**14**), 2-cycloheptenone (**9**) was converted into 2-[(trimethylsilyl)-oxy]-1,3-cycloheptadiene (**10**) via the kinetic enolate (94%) (Scheme II). Cyclopropanation of **10** and hydrolysis of the silyl ether afforded the stable bicyclic α,α-dichlorocyclopropanol **11** (96%). Treatment of the intermediate **11** with excess methylamine effected base-catalyzed rearrangement to 2-chloro-2,7-cyclooctadienone (**12**), which was rapidly consumed in methylamine conjugate addition (46%). 2β-Chloropseudopelletierine (**13**) was converted into pseudopelletierine (**14**) by reduction with tributyltin hydride (94%). The in situ generation of the cyclooctadiene substrate **12** circumvents difficulties encountered in preparation of the des-chloro substance by alternate procedures.[10]

This 2-cyclohexenone to 3-tropinone conversion is efficient in its yield and direct in its synthetic manipulation. In addition, the facile and regiospecific transformation of the α-chloro ketone moiety into olefin,[11] epoxide,[12] and

(2) For recent synthetic work see: (a) J. J. Tufariello, G. B. Mullen, J. J. Tegler, E. J. Trybulski, S. C. Wong, and S. A. Ali, *J. Am. Chem. Soc.*, **101**, 2435 (1979); (b) Y. Hayakawa, Y. Baba, S. Makino, and R. Noyori, *ibid.*, **100**, 1786 (1978); (c) R. L. Clarke and M. Heckler, *J. Org. Chem.*, **41**, 4586 (1976); (d) J. Mann, *J. Chem. Soc., Perkins Trans.* 1, 1564 (1978). For earlier synthetic work see: (e) R. L. Clark in "The Alkaloids", Vol. XVI, R. H. F. Manske, Ed., Academic Press, New York, 1977.

(3) For synthetic schemes utilizing or referring to 2,6-cycloheptadienone bisconjugate amine addition see: (a) Y. Kashman and S. Cherkez, *Synthesis*, 885 (1974); (b) A. T. Bottini and J. Gal, *J. Org. Chem.*, **36**, 1718 (1971); (c) T. Sato, K. Sato, and T. Mukai, *Bull. Chem. Soc. Jpn.*, **44**, 1708 (1971); (d) R. Robinson, *J. Chem. Soc.*, 111, 762 (1917).

(4) For recent structure–activity work see: (a) S. Cherkez, H. Yellin, Y. Kashman, B. Yaavetz, and M. Sokolovsky, *J. Med. Chem.*, **22**, 18 (1979); (b) Y. Kashman, S. Cherkez, and H. Yellin, *Chem. Abstr.*, **87**, P84847 (1977); (c) ref 2e.

(5) T. L. Macdonald, *J. Org. Chem.*, **43**, 4241 (1978).

(6) For synthesis of 2,6-cycloheptadienones see: (a) H. Takaya, Y. Hayakawa, S. Makino, and R. Noyori, *J. Am. Chem. Soc.*, **100**, 1778 (1978); (b) H. J. Reich, J. M. Renga, and I. L. Reich, *ibid.*, **97**, 5434 (1975); (c) K. Takenchi, K. Yasuda, and K. Okamoto, *Chem. Lett.*, 715 (1976); (d) E. Garbish, *J. Org. Chem.*, **20**, 2109 (1965); (e) A. J. Birch, G. M. Iskander, B. I. Magbord, and F. Stansfield, *J. Chem. Soc. C.*, 358 (1967).

(7) G. M. Rubottom and J. M. Gruber, *J. Org. Chem.*, **42**, 1051 (1977).

(8) The configuration at the chlorine-bearing carbon in **5** is based on spectral evidence [NMR ($J_{H_1-H_2}$ = 4.0 Hz)[9a] and IR (ν_{max} (C=O) 1725 cm^{-1})] and by analogy with the known 2β-bromotropinone.[9b] Evidence for formation of the α-chlorotropinone epimer derives from the presence of a downfield NMR resonance [NMR δ 4.94, broad singlet] observed in reactions conducted in NMR tubes [relative integrations: δ 4.94 (α-chlorotropinone) (0.4 H), 4.70 (β-chlorotropinone) (0.64 H), 2.56 (tropinone=NMe) (3.0 H)]. Upon workup, this downfield resonance disappears yielding a spectrum and an integration pattern consistent with a single β-chloro ketone epimer. In addition, these NMR experiments demonstrated that the initial amine addition occurred at the non-chloro-substituted olefin.

(9) (a) J. Feeney, R. Foster, and E. A. Piper, *J. Chem. Soc., Perkin Trans. 2*, 2016 (1977); (b) A. Nikon, *J. Am. Chem. Soc.*, **77**, 4094 (1955).

(10) H. O. Krabbenhoft, *J. Org. Chem.*, **43**, 4558 (1978).

(11) P. S. Wharton, S. Dunny, and L. S. Krebs, *J. Org. Chem.*, **29**, 958 (1964).

Table I. Physical Data for Products from the Tropinone Analogue and Pseudopelletierine Synthesis

compd	physical characteristics	IR (neat), cm^{-1}	NMR ($CDCl_3$, Me_4Si), δ	MS *m/e* (rel abundance)
4 (R = Me; R′ = H)	light oil, solid at 0 °C	1660, 1640, 1620, 900	7.24 (t, *J* = 3.5 Hz, 1 H), 6.32 (s, 1 H), 2.60 (9, 1 H), 2.08 (9, 3 H)	156 (28), 139 (51), 121 (76), 93 (100), 57 (22)
4 (R = Me; R′ = isopropyl)	light oil, mp ~10 °C	1665, 1640, 870	7.40 (d, *J* = 4.0 Hz, 1 H), 6.25 (s, 1 H), 4.95 (s, 2 H), 2.50 (br s, 3 H), 2.00 (s, 3 H), 1.71 (s, 3 H)	196 (36), 179 (21), 161 (100), 133 (53)
5 (R = Me; R′ = H)	light oil, thermally unstable	1715, 1115	4.70 (d, *J* = 4.0 Hz, 1 H), 3.62 (m, 2 H), 2.54 (s, 3 H), 1.15–2.95 (br m, 6 H), 1.20 (s, 3 H)	187 (17), 124 (43), 110 (49), 96 (100)
5 (R = Me; R′ = isopropenyl)	light oil (as 3:1 mixture of β:α-isopropenyl configurations)	1705, 1660 (w)	4.95 (s, 2 H), 4.78 (d, *J* = 4.0 Hz, 1 H), 3.65 (m, 1 H), 2.50 (s, 3 H), 1.20–2.95 (br m 5 H), 1.65 (3) and 1.62 (1) (s, 3 H), 1.22 (s, 3 H)	227 (31), 150 (62), 136 (100)
7	white solid, mp ≃ 10 °C	1720	3.58 (m, 1 H), 2.48 (s, 3 H), 1.30–2.80 (br m, 8 H), 1.20 (s, 3 H)	153 (44), 109 (60), 96 (100), 95 (100), 56 (94)
8	light oil (as 3:1 mixture of β-:α-isopropenyl configurations)	1715, 1645 (w)	4.95 (s, 2 H), 3.60 (m, 1 H), 2.45 (s, 3 H), 1.10–2.80 (br m, 5 H), 1.63 (3) and 1.58 (1) (s, 3 H), 1.20 (s, 3 H)	194 (30), 149 (82), 136 (100)
11	waxy solid, mp ≃ 18–20 °C	3350, 1645	5.8 (s, 2 H), 3.4 (s, 1 H, OH), 1.0–2.6 (br, m, 7 H)	156 (85), 128 (92), 108 (100), 92 (95), 80 (69)
13	white solid, mp < 35 °C	1720	4.75 (d, *J* = 80 Hz, 1 H), 3.60 (m, 2 H), 2.62 (s, 3 H), 1.20–3.05 (br m, 10 H)	

trimethylsilyl enol ether[13] groups expands the synthetic utility of these intermediates and indicates substantial potential in tropane modification. Thus, the ready availability and structural diversity possible in the 2-cyclohexenone component and the wide synthetic versatility of the regiospecifically generated 2-chlorotropinone intermediate make this sequence an attractive complement to existing schemes for tropane alkaloid synthesis.[2,3]

A standard experimental procedure is included below. Physical data for central compounds other than the intermediates in the 3-tropinone **6** synthesis are included in Table I.

Experimental Section

General. Proton magnetic resonance spectra were recorded at 100 MHz with a Jeol JNM-MH-100 spectrometer employing tetramethylsilane as an internal standard. Low-resolution mass spectra were obtained by direct insertion with an LKB 9000 spectrometer at 70 eV. The parent ion and the most intense peaks (2–4) are reported. Infrared spectra were obtained on a Perkin-Elmer 727 infrared spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. For column chromatography, E. Merck (type 60) silica gel or Florisil (100 mesh) and short column techniques were utilized, and for TLC analysis, E. Merck Silica Gel 60, F-254 precoated (0.25 mm) plates were employed. Calcium chloride was used as the drying agent throughout, and all experimental procedures were performed under an atmosphere of dry nitrogen.

2-Chloro-2,6-cycloheptadienones 3 and Bicyclic Alcohol 11. 2-[(Trimethylsilyl)oxy]-1,3-cyclohexadiene (**2**) (0.828 g, 4.93 mmol) (R = R′ = H) (prepared in 80% yield from 2-cyclohexenone (**1**) as described by Rubottom[7]) was dissolved in anhydrous dimethoxyethane (12 mL). Anhydrous sodium trichloroacetate (1.480 g, 7.93 mmol) was introduced and the suspension refluxed for 1.5 h.[5] The solution was cooled and then immediately subjected to hydrolysis for 2.0 h [methanol (80 mL)–10% (by volume) aqueous hydrochloric acid (20 mL)]. Ethereal workup and then chromatography [silica gel; ethyl acetate (12%)–petroleum ether (88%)] afforded 2-chloro-2,6-cycloheptadienone (**4**) (R = R′ = H) as a light oil: mp 8–11 °C (0.511 g, 73%); ^1H NMR ($CDCl_3$) δ 2.5 (t, *J* = 4.0 Hz, 4 H), 6.20 (d, *J* = 12.5 Hz, 1 H), 6.72 (m of d, *J* = 12.5 Hz, 1 H), 7.12 (m, 1 H); IR (neat) ν_{max} 1655, 1635, 790 cm^{-1}; MS *m/e* (rel intensity) 142 (51), 125 (35), 107 (79), 79 (100). Anal. Calcd for C_7H_7C1O: C, 58.9; H, 4.95. Found: C, 59.2; H, 4.88.

In an identical procedure, enolsilyl ether **2** (R = Me; R′ = H) (0.904 g, 5.00 mmol) derived in 97% yield from 3-methylcyclohexenone[7] was converted into 2-chloro-5-methylcycloheptadienone (**4**) (R = Me; R′ = H) (0.589 g, 3.45 mmol, 69%); enolsilyl ether **2** (R = Me, R′ = isopropenyl) (1.152 g, 5.05 mmol) obtained in 93% yield from carvone[7] was converted into 2-chlorocycloheptadienone (**4**) (R = Me; R′ = isopropenyl) (0.772 g, 3.94 mmol, 78%); and enolsilyl ether **10** (0.846 g, 4.55 mmol) obtained in 94% yield from 2-cycloheptenone[7] was transformed into the bicyclic alcohol **11** (0.834 g, 4.37 mmol, 96%).

(12) F. G. Bordwell, R. R. Frame, and J. G. Strong, *J. Org. Chem.*, **33**, 3385 (1968).

(13) G. M. Rubottom, R. C. Mott, and D. S. Kruger, *Synth. Commun.*, **7**, 327 (1977).

(14) We have observed that the use of commercial, technical grade sodium trichloroacetate substantially lowers the yield (and precipitates extensive polymer formation) in this reaction. For an alternate means for dichlorocyclopropanation of silyl enol ethers, utilizing phase transfer methods, see the work of Torii et al.[15]

(15) S. Torii, T. Okamoto, and N. Neno, *J. Chem. Soc., Chem. Commun.*, 293 (1978).

2β-Chloro-3-tropinones 5 and 2β-Chloropseudopelletierine (13). 2-Chloro-2,6-cycloheptadienone (4) (R = R′ = H) (0.510 g, 3.60 mmol) was dissolved in methanol (20 mL) and cooled to 0 °C. Aqueous methylamine (1.40 mL of a 12.9 M aqueous solution, 18.1 mmol) was introduced via syringe and the temperature maintained for 1.0 h, then the reaction mixture was partitioned between methylene chloride and water. The aqueous phase was reextracted with methylene chloride, then the combined organics were dried over calcium chloride and the solvent removed in vacuo. Chromatography [Florisil, ether (75%)–petroleum ether (25%)] afforded 2β-chloro-3-tropinone (5) (R = R′ = H) as a light oil (which solidifies at 0 °C) (0.386 g, 62%): ^{1}H NMR ($CDCl_3$) δ 1.65–2.05 (7, 4 H), 2.42 (d, d, J = 15.5 and 2.0 Hz, 1 H), 2.59 (s, 3 H), 2.80 (d, d, J = 15.5 and 4.0 Hz, 1 H), 3.60 (m, 2 H), 4.70 (d, J = 4.0 Hz, 1 H); IR (neat) ν_{max} = 1725, 1140 cm^{-1}; MS m/e (rel intensity) 173 (24.3), 110 (39), 96 (48), 82 (100).

Utilizing identical experiment procedures, 2-chlorocycloheptadienone (4) (R = Me; R′ = H) (0.589 g, 3.45 mmol) was transformed into 2β-chloro-5-methyltropinone (5) (R = Me; R′ = H) (0.424 g, 2.28 mmol, 66%); 2-chlorocycloheptadienone (4) (R = Me; R′ = isopropenyl) (0.770 g, 3.94 mmol) was converted into the tropinone analogue 5 (R = Me; R′ = isopropenyl) (0.442 g, 1.93 mmol, 49%); and bicyclic alcohol 11 (0.834 g, 4.37 mmol) was converted into 2β-chloropseudopelletierine (13) (0.379 g, 2.01 mmol, 46%).

3-Tropinones 6, 7, and 8 and Pseudopelletierine (14). 2β-Chloro-3-tropinone (5) (R = R′ = H) (0.386 g, 2.23 mmol) was dissolved in benzene (10 mL) to which tri-n-butyltin hydride (2.00 g, 7.0 mmol) and azoisobutyronitrile (~30 mg) were added. The solution was refluxed until consumption of starting material was complete (~1 h), then the reaction was cooled and partitioned between 10% aqueous hydrochloric acid and ether. The pH of the aqueous layer was adjusted to 10 and the aqueous layer extracted with methylene chloride twice. The organics were dried over calcium chloride, and the solvent was removed in vacuo. Filtration of the residue through Florisil gave (±)-tropinone (6) (R = R′ = H) (0.158 g, 70%) identical in spectral and physical characteristics with an authentic sample.

With the use of an identical experimental procedure, chlorotropinone (5) (R = Me; R′ = H) (0.586 g, 3.45 mmol) was dechlorinated to yield tropinone analogue 7 (0.284 g, 1.79 mmol, 52%); chlorotropinone (5) (R = Me; R′ = isopropenyl) (0.442 g, 1.93 mmol) was reduced to isomeric tropinone analogues 8 (0.215 g, 1.09 mmol, 56%); and chloropseudopelletierine 13 (0.379 g, 2.01 mmol) was transformed into pseudopelletierine (0.284g, 0.190 mmol, 94%), identical in physical and spectral characteristics with an authentic sample.

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Rearrangement-Hydrolysis of 5-Amino-1,2,4-Benzothiadiazines[1]

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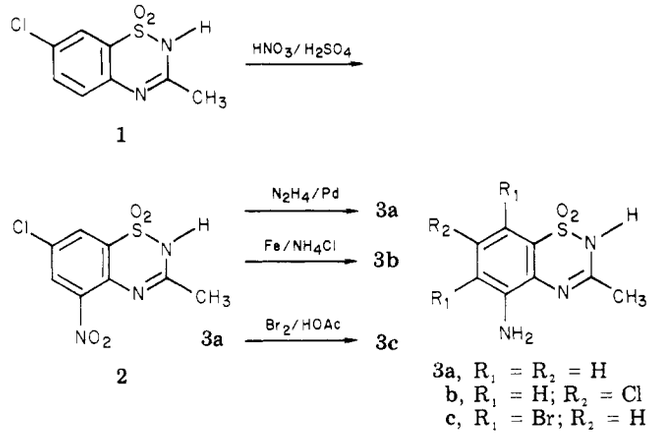
Several compounds are known which exert a biological action on the pancreas and thus have been chosen for study as diagnostic radioactive pancreatic imaging agents.[2] 7-Chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (1) and closely related analogues are known hyperglycemics which appear to have a direct pancreatic effect.[3] Studies in our laboratory directed to the preparation of radioiodinated 1,2,4-benzothiadiazines for study in hamsters bearing pancreatic tumors[4] have uncovered a unique rearrangement–hydrolysis induced by diazotization of 5-amino-1,2,4-benzothiadiazine 1,1-dioxides.

Nitration of 1 in warm nitric/sulfuric acid gave 5-nitro-7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (2) in 64% yield. Reduction of the nitro group by



hydrazine, palladium, and ethanol effected a simultaneous dehalogenation to 5-amino-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (**3a**). Iron–ammonium chloride reduction of **2** gave the chloro-containing amine (**3b**), while direct bromination of **3a** gave the 6,8-dibromo analogue (**3c**) in 57% yield.

Diazotization and iodination of **3a–c** by standard Sandmeyer methods gave products lacking iodine but possessing, by elemental analysis and mass spectral measurement, the elements of the diazo function and 1 equiv of water. The methyl ^{1}H NMR signals of the diazotized products revealed an upfield shift of approximately 0.4 ppm in each case. Furthermore, the ready solubility of the products in dilute base and the typical primary sulfonamide N–H bands[5] at 3085–3350 cm^{-1} implicated the presence of the SO_2NH_2 group. A sharp carbonyl absorption was also evident in these diazotized products at 1718–1728 cm^{-1} and taken with the 43 amu base peak in their mass spectra pointed to the presence of an acetyl function. The 1-acetylbenzotriazoles (**5a–c**) represent structural entities in accord with the available spectral and physical data.

The reported C=O stretch for similar 1-acetylbenzotriazoles is a uniquely similar high wavenumber absorption to that detected in the diazotized derivatives of **3a–c**.[6] In addition, support for the assignment of structures **5a–c** to the product can be found in the successive mass spectral fragmentation of 42 and 28 amu from the parent ions. Sequential loss of a ketene equivalent and nitrogen characterize the published cracking patterns of other 1-acetylbenzotriazoles.[7]

A logical pathway for the reaction would be interception of the intermediate diazonium function by N-4 of the

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(4) For a typical study of this type on other candidate agents see: V. R. Risch, T. Honda, N. D. Heindel, J. L. Emrich, and L. W. Brady, *Radiology*, **124**, 837 (1978).

(5) Sadtler Standard Grating Spectra No. 10670K and 15929K, 1968.

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