

A VERSATILE NEW STRATEGY FOR THE SYNTHESIS OF TROPONES

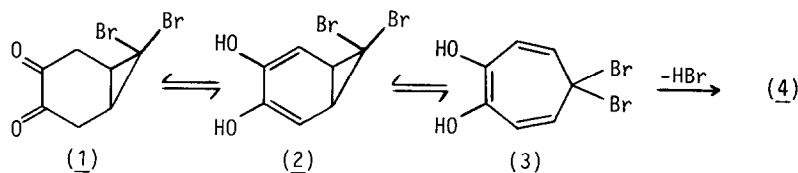
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Summary: Swern-type oxidation of various 7-halogenobicyclo[4.1.0]heptane-2,3- or -3,4-diols affords the corresponding bicyclic diketones which undergo *in situ* ring expansion and loss of hydrogen halide to give α -tropolones in high yield. The quantitative conversion of the isolable 1,4-diketone 26 into the γ -tropolone acetate 27 has been achieved.

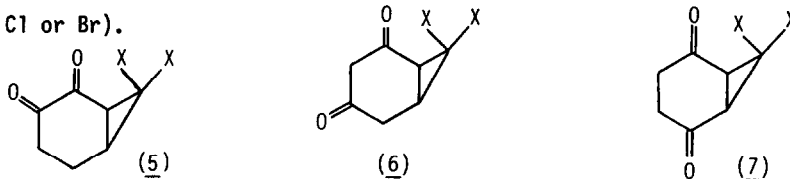
Despite the continued interest in the chemistry of tropolones (hydroxycycloheptatrienones) and their derivatives,¹ the development of a general route¹⁻³ to these non-benzenoid conjugated carbocycles remains a challenging problem.^{2,3} The recent isolation of the complex tropolone natural products Grandirubrine,⁴ Imerubrine,⁴ and Manicol⁵ and the resulting interest in their total synthesis⁴ serves to emphasize the need for mild, efficient, regio-controlled, and direct methods for the construction of this ring system. Herein, we describe a new synthesis of tropolones which has these attributes and proceeds from readily accessible starting materials.

On the basis of our earlier observations⁶ that 7-halogenobicyclo[4.1.0]heptenones are excellent precursors to tropolones (cycloheptatrienones) we decided to investigate the possibility that 7-halogenobicyclo[4.1.0]heptanediones might undergo comparable ring-expansion reactions to give tropolones. Consider, for example, the bicyclic diketone 1. Two-fold keto to enol tautomerisation of this compound would give the



norcaradiene 2 which on electrocyclic ring-opening^{2,6} would produce the cycloheptatriene 3. Loss of the elements of hydrogen bromide from 3 should then afford 5-

bromotropolone (4). Related processes can be envisaged for bicyclic diketones of the type 5 - 7 ($X = \text{Cl}$ or Br).



The oxidation of the corresponding diols appeared to offer a direct route to the required diketones and the results of this approach are shown in the table.⁷ Thus, treatment of the *vic*-diols 8 - 10^{8a} under Swern-type oxidation conditions⁹ [2.0 - 3.0 mol. equiv. $(\text{CF}_3\text{CO})_2\text{O}$, ≥ 3.0 mol. equiv. $(\text{CH}_3)_2\text{SO}$, -60°C , 1.5 h; then *ca.* 7.0 mol. equiv. $(\text{CH}_3\text{CH}_2)_3\text{N}$, -60°C , 1.5 h] afforded the tropolones 19¹⁰ 20, and 21, respectively, in high yield. This oxidation procedure does not appear to be sensitive to the geometry of the hydroxyl groups, since analogous treatment of each of the isomeric diols 11,^{8a} 12,^{8b} and 13^{8b} gave tropolone 4¹¹ in similar yield. Oxidation of compound 14^{8b} delivered β -thujaplicin (22)^{1a}. Evidence for the intermediacy of 7-halogenobicyclo[4.1.0]heptane-3,4-diones (e.g. 1) in these conversions stems from the observation that treatment of the tricyclic diol 15^{8a} under the same conditions yields the α -hydroxy enone 23. Reaction of diol 16^{8a} with 2.1 equivalents of the Swern-oxidant afforded the mono-enolic tautomer 24 of α -diketone 5 ($X = \text{Br}$) as well as tropolone 25.¹² In contrast, treatment of compound 16 with 4.1 equivalents of the same oxidant gave 25 exclusively.

While attempts to prepare the bicyclic 1,3-diketone 6 ($X = \text{Cl}$) (and thence the corresponding β -tropolone) by oxidation of the 1,3-diol 17^{8b} have not been successful, the isolable 1,4-diketone 26 was readily obtained by oxidation (3.6 equiv. pyridinium chlorochromate, CH_2Cl_2 , 20°C , 18h, 100%) of diol 18.^{8b} Treatment of compound 26 under conditions employed for enol-acetate formation¹³ [$(\text{CH}_3\text{CO})_2\text{O}$, CH_2Cl_2 , 1 drop 60% aqueous HClO_4 , 20°C , 3 h] afforded the γ -tropolone acetate 27 (100%) (m.p. = $55\text{-}56^\circ\text{C}$) presumably *via* intermediate 28.

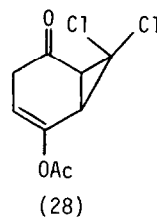
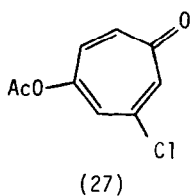
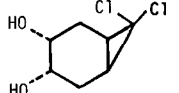
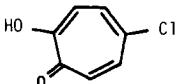
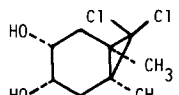
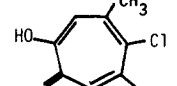
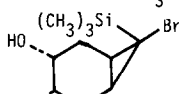
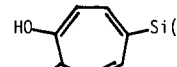
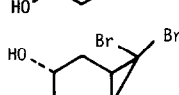
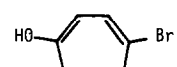
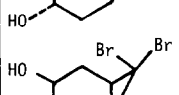
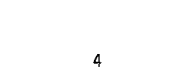
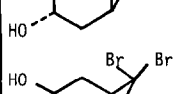

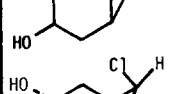
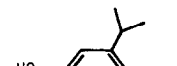
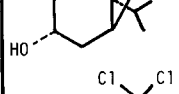
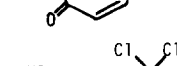
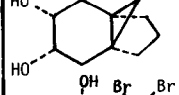
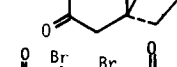
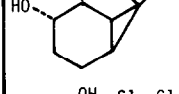

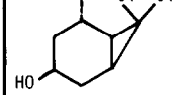
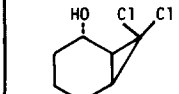
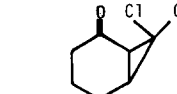
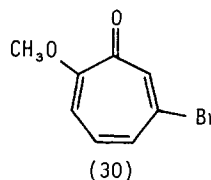
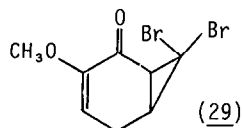


Table: Oxidation Reactions ^a of 7-Halogenobicyclo[4.1.0]heptanediols			
Diol	Product(s)	Yield ^b (%)	m.p. data (°C) diol; product(s)
		79	138-139; 180-182 (sealed tube), lit. ¹⁰ 180-182
		92	145-146; 157-158
		81	155-156.5; 115.5-117
		75	142-143; 192-193 (sealed tube), lit. ¹¹ 189-190
		73	102-103
		75	103-103.5
		78	oil; oil
		86	125.5-127; 131-133
		73:13 ^c 0:90 ^d	73-74.5; 112-114; 86-87, lit. ¹² 85-86
			147-149
	complex mixture		
		100	123-123.5; 56.5-57.5

^a See text for oxidation conditions. ^b Of isolated, pure products.

^c Using 2.1 equiv. of oxidant. ^d Using 3.1 equiv. of oxidant.

The formation of both possible α -tropolone alkyl ethers on alkylation of unsymmetrical tropolones is a well-known phenomenon,¹ and represents a long-standing problem in the regio-controlled synthesis of various troponoid compounds including colchicine.^{2,3} The following extension of the present work suggests a useful solution to this problem. Thus, methylation [K_2CO_3 , $(CH_3)_2CO$, $(CH_3)_2SO_4$, 20°C, 5.0 h] of compound 24 afforded α -methoxy enone 29 (90%) (m.p. 90-92°C) which underwent base-promoted (K_2CO_3 , CH_3OH , 20°C, 1.0 h) conversion into the α -tropolone methyl ether 30 (80%) (m.p. = 129.5-131.5°C; lit.¹⁴ 130-131.5°C).¹⁵



We are attempting to apply these observations to the synthesis of various structurally interesting troponoid compounds including colchicine. Results will be reported in due course.

References and Notes

1. For a general introduction to the chemistry of these compounds see: (a) D. Lloyd, 'Non-benzenoid Conjugated Carbocyclic Compounds' Elsevier, Amsterdam, 1984; (b) F. Pietra, *Acc. Chem. Res.*, **1979**, 12, 132; (c) F. Petra, *Chem. Rev.*, **1973**, 73, 293; and references therein.
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7. Satisfactory spectral, microanalytical, and/or accurate mass data were obtained for all new compounds or suitable derivatives thereof.
8. (a) Prepared by the osmium tetroxide catalysed dihydroxylation (*Tetrahedron Lett.*, **1980**, 21, 449) of the corresponding olefin. (b) This compound was prepared by conventional methods from known starting materials; experimental details will be published in a forthcoming full paper.
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15. In contrast, methylation [CH_2N_2 , $(CH_3CH_2)_2O$, 20°C] of the α -tropolone 25 affords a ca. 1:1 mixture of 30 and its regio-isomer.

(Received in UK 3 July 1985)