Chemistry of 1,2,4-Trioxanes. Formation of 1,2-Diol Monoesters

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1,2,4-Trioxanes bearing a hydrogen substituent at the C-3 position when treated with triethylamine undergo scission of the oxygen–oxygen bond to give the corresponding 1,2-diol monoesters in high yields; similar treatment of a bridged bicyclic 1,2,4-trioxane afforded the related γ-hydroxy-δ-lactone and its isomeric spirocyclic γ-lactone in 90% yield.

Apart from instances of the fragmentation of 1,2,4-trioxanes[1] and rearrangements of the potent antimalarial Qinghaosu,[2] scarcely any systematic chemistry of this little-known class of heterocycles has been reported.[3,4] Recently we have developed methods for preparing 1,2,4-trioxanes from 1,4-endoperoxides,[5,6] 1,2-dioxetanes,[6,7] allylic hydroperoxides,[8] and electron-rich alkenes.[9] Consequently, many trioxanes of various types are now available for study.

We now describe a new reaction of 1,2,4-trioxanes in which treatment with base converts them stereospecifically into 1,2-diol monoesters. By way of illustration bicyclic trioxanes[5] (**1**)—(**6**) and a bridged bicyclic derivative[10] (**13**) were chosen. The procedure is simple; the appropriate trioxane as a 0.1 M solution in 30% Et_3N–CH_2Cl_2 (1—4 ml) is allowed to stand at room temperature until no further reaction is detected by t.l.c. The resulting reaction mixture is purified by preparative layer chromatography on silica gel. The reactions are remarkably clean; in addition to the desired products which are obtained in high yield (45—96% yield, Table 1), only the starting trioxane is recovered. An exception is the parent trioxane (**5**). It affords 1,4-dimethyl-2-naphthol (**12**)[11] as well as the formate (**11**) from which it presumably derives by decarboxylative dehydration. In all products (**7**)—(**11**), the configuration of the vicinal hydroxy and carboxylate groups remains the same as that of the parent trioxane, namely *cis*.

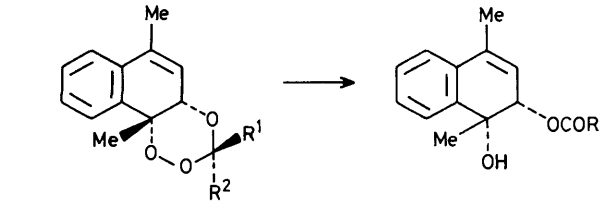
The reaction undoubtedly proceeds by abstraction of the C-3 proton as attested by the comparative rapidity of cleavage of the *p*-nitrophenyl derivative (**3**) in which the stability of the resulting anion is enhanced. When the C-3 hydrogen substituent is absent, as is the case for the *gem*-dimethyl derivative (**6**), no reaction occurs even when (**6**) is heated with aqueous sodium hydroxide for several days.

The *trans* bridged bicyclic trioxane (**13**) on treatment with Et_3N–CH_2Cl_2 gives the benzocoumarin derivative (**14**)

Table 1. The triethylamine-catalysed cleavage of some 1,2,4-trioxanes.[a]

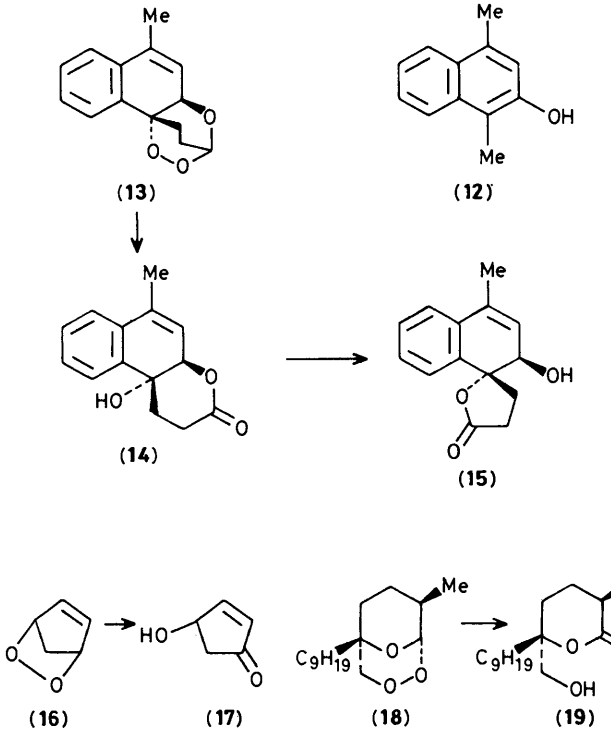
Trioxane	Reaction time (days)	Cleavage[b] product (% yield)	% Yield of recovered trioxane
(**1**)	9	(**7**) (67)	26
(**2**)	8	(**8**) (82)	12
(**3**)	1	(**9**) (96)	0
(**4**)	9	(**10**) (78)	9
(**5**)	5	(**11**) (45)[c]	0
(**13**)	15 min	(**14**) + (**15**) (90)	0

[a] All reactions were carried out at 25 °C except last entry (−5 °C). [b] All new compounds (**7**)—(**11**), and (**14**), (**15**) gave satisfactory analytical and spectral data. [c] In addition to (**11**), the naphthol (**12**) was isolated in 40% yield.



(1) R^1 = H, R^2 = Ph
(2) R^1 = H, R^2 = C_6H_4Cl-*p*
(3) R^1 = H, R^2 = $C_6H_4NO_2$-*p*
(4) R^1 = Me, R^2 = H
(5) R^1 = R^2 = H
(6) R^1 = R^2 = Me

(7) R = Ph
(8) R = C_6H_4Cl-*p*
(9) R = $C_6H_4NO_2$-*p*
(10) R = Me
(11) R = H



(13) (12) (14) (15)

(16) (17) (18) (19)

together with its spirocyclic isomer (**15**) in a 3:1 ratio.† Undoubtedly, the product first formed is (**14**). Subsequent isomerization to (**15**) occurs by trans-lactonization.[12] Significantly, the configuration of the hydroxy group and the lactone attachment remains *trans* in both isomers.

The cleavage of the trioxane ring is mechanistically reminiscent of the base-catalysed isomerization[13] of cyclopent-2-ene 1,4-endoperoxide (**16**) to 4-hydroxycyclopent-2-en-1-one (**17**) which is of synthetic relevance.[14] Similarly, 1,2,4-trioxanes, easily obtainable by a variety of methods, offer a potentially useful approach to 1,2-diol monoesters and lactones. Many natural products contain such entities.[15] An example is malyngolide (**19**)[16] which should be accessible from its related trioxane (**18**).

† I.r.(CH_2Cl_2): ν_{CO} = 1740 and 1778 cm^{-1} for (**14**) and (**15**) respectively.

We thank the Swiss National Science Foundation and the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases for support of this work.

Received, 12th August 1985; Com. 1208

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