Synthesis of 1,4-Disubstituted (or 1,4,4-Trisubstituted) 2,3,5,6,11-Pentaoxabicyclo[5.3.1]undecanes

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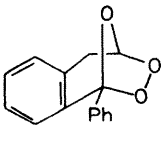
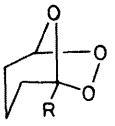
Summary The reaction of a mixture of bicyclic ozonides (trioxolans), carbonyl compounds, and hydrogen peroxide in the presence of catalytic amounts of chlorosulphonic acid gives the corresponding 2,3,5,6,11-pentaoxabicyclo[5 3 1]undecanes in 3—35% yield

SYNTHESIS of cyclic peroxides with new structures has attracted great attention because of their unique properties including chemiluminescence and biological activity.[1-3]

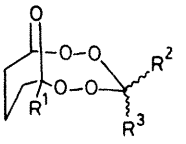


(1)



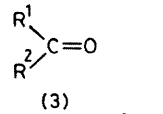
(2)

a; R = Ph
b; R = Me



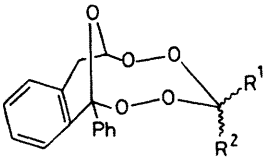
(4)

a, R^1 = Ph, R^2 = *p*-tolyl, R^3 = H
b; R^1 = Ph, R^2 = pentyl, R^3 = H
c; R^1 = Ph, R^2R^3 = -$[CH_2]_5$-
d; R^1 = Ph, R^2 = R^3 = Me
e; R^1 = Me, R^2 = *p*-tolyl, R^3 = H
f; R^1 = Me, R^2 = pentyl, R^3 = H
g; R^1 = Me, R^2R^3 = -$[CH_2]_5$-
h; R^1 = R^2 = R^3 = Me
i, R^1 = Ph, R^2 = $PhCO[CH_2]_3$, R^3 = H



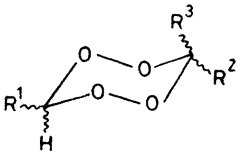
(3)

a; R^1 = *p*-tolyl, R^2 = H
b; R^1 = pentyl, R^2 = H
c, R^1R^2 = -$[CH_2]_5$-
d; R^1 = R^2 = Me



(5)

a; R^1 = *p*-tolyl, R^2 = H
b; R^1 = pentyl, R^2 = H
c; R^1R^2 = -$[CH_2]_5$-
d; R^1 = R^2 = Me



(6)

a; R^1 = $PhCO[CH_2]_3$, R^2 = *p*-tolyl, R^3 = H
b; R^1 = $PhCO[CH_2]_3$, R^2 = R^3 = Me
c; R^1 = R^2 = *p*-tolyl, R^3 = H

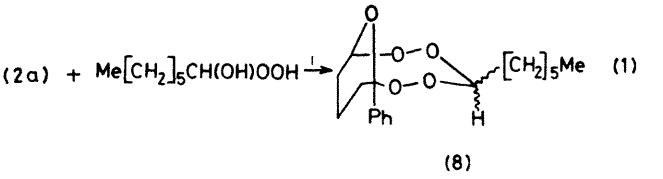
$PhCO[CH_2]_3CO_2H$

(7)

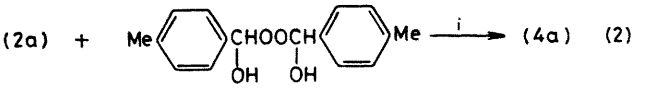
Reagents: i, $ClSO_3H$ (0·1 equiv.) in AcOH, 20 °C, 20 min.

Recently we reported that the reaction of 1-phenyl-6,7,8-trioxabicyclo[3.2.1]octane (**2a**) with catalytic amounts of chlorosulphonic acid gives the pentaoxabicycloundecane (**4i**).[4,5] We now report a widely applicable synthetic route to bicyclic peroxides with this unique structure. Reaction of a mixture of the ozonides (**1**), (**2a**), or (**2b**), the carbonyl compounds *p*-tolualdehyde (**3a**), hexanal (**3b**), cyclohexanone (**3c**), or acetone (**3d**), and 28% aqueous hydrogen peroxide in the presence of chlorosulphonic acid gives the corresponding pentaoxabicycloundecanes (**4a—d**) from (**2a**), (**4e—h**) from (**2b**), and (**5a—d**) from (**1**) with (**3a**), (**3b**), (**3c**), and (**3d**), respectively. In the reactions of (**2a**) with (**3a**) or (**3d**), the crossed tetroxans (**6a**) and (**6b**), respectively, were also obtained (Table).† The following experimental procedure illustrates the method.

A solution of (**2a**) (3 mmol), (**3a**) (3 mmol), 28% aqueous hydrogen peroxide (3 mmol), and chlorosulphonic acid (0·3 mmol) in acetic acid (30 ml) (the reagents were added to acetic acid in this order within 1 min) was stirred at 20 °C for 2 h. After conventional work-up the neutral products were isolated by column chromatography on silica gel using ether–benzene–light petroleum as eluant (the solvent polarity was gradually increased by increasing the proportion of ether). The first fraction contained *trans*-3,6-di-*p*-tolyl-1,2,4,5-tetroxan (**6c**)[6] (3%), from the second fraction the pentaoxabicyclo[5.3.1]undecane (**4a**) was obtained in 15% yield, the third fraction contained the tetroxan (**6a**) (3%), and from the final fraction (**4i**) was



(2a) + $Me[CH_2]_5CH(OH)OOH$ → (8) (1)



(2a) + (4a) (2)

TABLE. Reaction of a mixture of the ozonides (**1**) and (**2**), the carbonyl compounds, (**3**) and hydrogen peroxide in the presence of chlorosulphonic acid.

Ozonide	Carbonyl compound	Reaction time/h	Crossed products [yield/ mol %]	M.p./°C	n.m.r., δ, 7-H
(**1**)	(**3a**)	4	(**5a**) [27]	199—201	6·07 (d, *J* 6 Hz)
(**1**)	(**3b**)	2	(**5b**) [13]	84—85	5·96 (d, *J* 6 Hz)
(**1**)	(**3c**)	2	(**5c**) [35]	125—128	5·90 (d, *J* 6 Hz)
(**1**)	(**3d**)[b]	2	(**5d**) [7]	144—146	5·96 (d, *J* 6 Hz)
(**2a**)	(**3a**)	2	(**4a**) [15]	145—147	5·76br. (s)
			(**6a**) [3]	110—111	6·11 (t, *J* 8 Hz)[a]
(**2a**)	(**3b**)	4	(**4b**) [22]	Oil	5·62br. (s)
(**2a**)	(**3c**)	2	(**4c**) [17]	140—142	5·60br. (s)
(**2a**)	(**3d**)[b]	4	(**4d**) [4]	134—135	5·60br. (s)
			(**6b**) [3]	66—68	5·42 (t, *J* 4·5 Hz)[a]
(**2b**)	(**3a**)	4	(**4e**) [23]	109—110	5·47br. (s)
(**2b**)	(**3b**)	4	(**4f**) [20]	Oil	5·38br. (s)
(**2b**)	(**3c**)	4	(**4g**) [7]	114—116	5·36br. (s)
(**2b**)	(**3d**)[b]	36	(**4h**) [10]	Oil	5·39br. (s)

[a] The absorption of 3-H. [b] Acetone was used as the solvent.

† In some cases two configurationally isomeric products (*exo* and *endo* in the case of the bicyclic peroxides, and *trans* and *cis* in the case of the tetroxans) can be formed. However, only one isomer was isolated in all the reactions The configurations of (**4b**), (**4f**), and (**5b**) were reasonably assigned as *exo* on the basis of the ^1H n.m.r. signals of 4-H (see the discussion in ref. 5). However, the configurations of (**4a**), (**4e**), (**5a**), and (**6a**) could not be determined.

obtained in 21% yield. 4-Benzoylbutyric acid (**7**) was also isolated in 19% yield.

Of relevance to the above results, the reaction of (**2a**) with 1-hydroxyheptyl hydroperoxide in the presence of chlorosulphonic acid gave the pentaoxabicycloundecane (**8**) in 15% yield [reaction (1)]. When a mixture of (**2a**) and bis-(α-hydroxy-4-methylbenzyl) peroxide was treated with chlorosulphonic acid, (**4a**) was obtained in 54% yield [reaction (2)].

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