Masking the Carboxy Group as a 2,6,7-Trioxabicyclo[2.2.2]octane: Application to the Synthesis of Alkylcobaloximes containing Ester and Carboxy Groups

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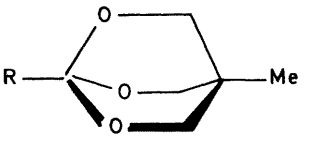
Summary The hydrolytic stability of 2,6,7-trioxabicyclo-[2 2 2]octanes towards aqueous acid is intermediate between that of 1,1,1-triethoxyethane and 1-methyl-2,8,9-trioxa-adamantane, a synthetic application of this trioxabicyclo-octane group as a masked carboxy function is described

THERE is a need for a method of protecting carboxylic acids and esters which masks their carbonyl group and abolishes reactivity towards bases and nucleophiles Orthoesters have been used for this purpose, but previously have suffered from the disadvantage of either being relatively inaccessible [*e g* orthoesters derived from *cis*-cyclohexane-1,3,5-triol,[1] 2-alkoxy-2-alkyl (or aryl)-benzoxathioles[2]] or being too labile (*e g* 1,1,1-triethoxyalkanes) Oxazolines have been recommended as masked carboxy functions, but are rather difficult to hydrolyse and retain reactivity towards strong bases and nucleophiles [3]

We have studied orthoesters {1-alkyl-4-methyl-2,6,7-trioxabicyclo[2 2 2]octanes (**1a**—**1c**) and (**2a**)} derived from 1,1,1-tris(hydroxymethyl)ethane, a cheap, commercially available triol [4] We found that the orthoesters (**1b**) and (**1c**) possess suitable hydrolytic stability for applications in synthesis, as illustrated by the preparation of the alkylcobaloxime (**2a**) and its conversions into the ester (**2c**) and the carboxylic acid (**2d**)

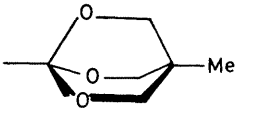
4-Chloro-1,1,1-triethoxybutane was prepared from 1-chloro-3-cyanopropane by the standard method[5] and was treated with an equimolar amount of 1,1,1-tris(hydroxymethyl)ethane in benzene (overnight reflux) to yield 66% of pure (**1b**),† b p 94—96 °C, 0 001 mmHg, ^{1}H n m r (CCl_4), δ 0·81 (s, CH_3), 1·71 (t, α-CH_2), 1·88 (m, β-CH_2), 3·51



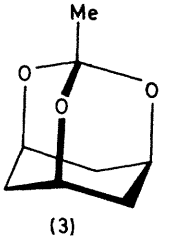
(1) a, R = Me
b; R = $[CH_2]_3Cl$
c, R = $[CH_2]_3I$

R Co(dmgH)$_2$py

(2) a, R = $[CH_2]_3$



b, R = $[CH_2]_3CO_2CH_2CMe(CH_2OH)_2$
c, R = $[CH_2]_3CO_2Me$
d; R = $[CH_2]_3CO_2H$



(3)

$(EtO)_3CR$

(4) a; R = Me
b, R = $[CH_2]_2CH_2Cl$

dmgH = monoanion of dimethylglyoxime, py = pyridine

† A satisfactory combustion analysis was obtained for this compound

(t, CH_2Cl), and 3·81 (s, OCH_2) An analogous method was used to prepare the orthoester (**1a**) [6] Treatment of (**1b**) with NaI (10 mol equiv) in dry acetone containing $NaHCO_3$ (5 mol equiv) gave 65% of (**1c**),† m p 41—42 °C, ^1H n m r (CCl_4), δ 0·79 (s, CH_3), 1·65 (t, α-CH_2), 1·94 (m, β-CH_2), 3·16 (t, CH_2I), and 3·79 (s, 3 × OCH_2)

The rates of hydrolysis of (**1a**) and (**1b**) were compared with those of the trioxa-adamantane (**3**),[7] 1,1,1-triethoxyethane (**4a**),[8] and 4-chloro-1,1,1-triethoxybutane (**4b**) giving the following order of reactivity [60/40 (v/v) dioxan–aqueous acetate buffer,[8] pH 4·48, 303 K] (**4a**), (**4b**) > (**1a**), (**1b**) ≫ (**3**) The half-lives for (**1a**) and (**1b**) under these conditions are 33·50 ± 0 03 and 107 2 ± 0 2 min, respectively Whereas (**4a**) is rapidly hydrolysed in pure water, (**1b**) suffers < 10% hydrolysis overnight at room temperature

Alkylcobaloximes and cobalamins containing an ester or carboxy function in their σ-alkyl group are required for studies of adenosylcobalamin-dependent enzymic reactions [9] Such compounds may be difficult to prepare from, *e g* halogenoacids by conventional methods [10] Not only is there the risk of, for example, lactonisation of a halogenoacid under the basic reaction conditions used, but the presence of an ionisable group in the σ-alkyl group may complicate isolation These problems are circumvented by approaching the ester or carboxy function *via* a 1-substituted 4-methyl-2,6,7-trioxabicyclo[2 2 2]octane [11,12]

The orthoester (**1c**) was treated with 1 mol equiv (pyridine)cobaloxime(I) [prepared by reducing bromo(pyridine)cobaloxime with $NaBH_4$ in ethanol]‡ for 16 h at room temperature to give (**2a**),† which was directly crystallised in a quantitative yield from the reaction mixture by addition of water containing 1% pyridine An analytical sample of (**2a**) was obtained by recrystallisation from chloroform ^1H n m r ($CDCl_3$), δ 0 75 (s, Me), 1·03 (m, $CoCH_2CH_2$), 1·55 (t, $CoCH_2$ and CH_2CO_3), 2 1 (4 × dmg Me), 3 83 (s, 3 × CH_2O), 7·3 (t, 2 × py β-H), 7·7 (t, py γ-H), and 8·50 (d, 2 × py α-H)

The cobaloxime (**2a**) in dichloromethane was stirred with 0 5 M aqueous hydrochloric acid (30 min, room temperature), to give, after neutralisation of the aqueous layer with Na_2CO_3, 82% of (**2b**),† ^1H n m r ($CDCl_3$), δ 0 84 (s, CH_3), 1·27 (m, $CoCH_2CH_2$), 1 54 (t, $CoCH_2$), 2 13 (s, 4 × dmg Me), 2·27 (t, CH_2CO), 3 55 (s, 2 × CH_2OH), 3 3—4 0 (br s, 2 × OH), 4·10 (s, CH_2OCO), 7 31 (t, 2 × py β-H), 7 73 (t, py γ-H), and 8 53 (d, 2 × py α-H) Methanolysis of (**2b**) using 13 equiv NaOMe in MeOH (2 min room temperature) gave 78% of the ester (**2c**) † Hydrolysis of (**2b**) with a 2-phase system (CH_2Cl_2–aqueous KOH) gave, after neutralisation of the aqueous layer and addition of pyridine, 62% of the acid (**2d**) †

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‡ Alternatively, (pyridine)cobaloxime(I) from disproportionating cobaloxime(II) in alkaline solution can be used

[1] H. Stetter and K H Steinacker, *Chem Ber* , 1954, **87**, 205
[2] G. Aimo, I Degani, and R Fochi, *Synthesis*, 1979, 223
[3] A. I Meyers and E D Mihelich, *Angew Chem Internat Edn* , 1976, **15** 270
[4] *Cf* R H DeWolfe, 'Carboxylic Ortho Acid Derivatives,' Academic Press, London, 1970, p 135
[5] S M McElvain and J W Nelson, *J Amer Chem Soc* , 1942, **64**, 1825
[6] *Cf* W von E Doering and L K Levy, *J Amer Chem Soc* , 1955, **77**, 509
[7] O Bouab, G Lamaty, and C Moreau, *J C S Chem Comm* , 1978, 678
[8] R H DeWolfe and J L Jensen, *J Amer Chem Soc* 1963, **85**, 3264
[9] B T Golding in 'Comprehensive Organic Chemistry, ed D Barton and W D Ollis, Pergamon, Oxford, 1979, Vol 5, Ch 24 4
[10] G N Schrauzer, *Inorg Synth* , 1968, **11**, 61
[11] Alkylcobaloximes substituted with an ester function at the 1-position of the σ alkyl group can be prepared by treating cobaloxime(II) with an α-halogenoester in the presence of zinc (P F Roussi and D A Widdowson, *J C S Chem Comm* , 1979, 810)
[12] ω-Carboxyalkylcobalamins can be prepared in very low yield (based on carboxylic acid) by treating a carboxylic acid with cob(II)alamin in the presence of vanadium(III) and an oxidant (G N Schrauzer and M Hashimoto, *J Amer Chem Soc* , 1979, **101**, 4593)