Photolytic Conversion of Some Bicyclo[3.2.0]heptanones into 3-Hydroxy- or 3-Methoxy-2-oxabicyclo[3.3.0]octan-2-ones

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The ketones (1) and (7)—(9) gave the corresponding cyclic acetals (3), (4), and (12)—(17), respectively, on photolysis in methanol. Concurrent production of the alkenes (6) and (18)—(20) detracted from the potential synthetic utility of this process. However, photolysis of the ketones (8), (10), and (11) in aqueous tetrahydrofuran or aqueous acetonitrile led to a highly selective ring-expansion process, and consequently high yields of the corresponding γ-lactols (21)—(23).

THE photochemistry of simple substituted cyclobutanones has been extensively investigated. The pioneering work by Turro [1] showed that the behaviour of the four-membered ring system on photolysis differed from that of larger ring systems in that the products were derived largely, if not exclusively, from the trapping of an intermediate oxacarbene.[2] In some instances the yields of the ring-expanded product(s) were almost quantitative. In addition to products derived from further reaction of the oxacarbene, cyclopropane derivatives (resulting from a decarbonylation reaction) and alkenes (formed from a retro [2 + 2] reaction) have been isolated on photolysis of some cyclobutanones (Scheme 1).

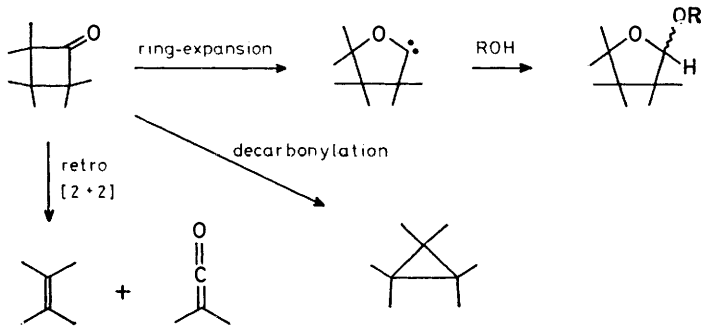
We were particularly interested in the photolytic behaviour of substituted bicyclo[3.2.0]heptanones which contain a cyclobutanone ring as part of the structure.[3] Difficulties encountered in the Baeyer–Villiger ring-expansion process for the conversion of some of these bicyclic ketones into 2-oxabicyclo[3.3.0]octan-3-ones, which were known prostaglandin intermediates,[4] led us to seek alternative processes for this key step. In this synthetic context, the ring-expansion process was required to take place in preference to the decarbonylation and cyclo-elimination pathways.

Earlier work had shown that the photolysis of bicyclo[3.2.0]hept-2-en-6-one led predominantly to the elimination of keten,[5] while 7-chlorobicyclo[3.2.0]heptan-6-ones furnished products of ring-contraction.[6]

However, the alkene and halogeno moieties that dictate the preferred pathway in the above photo-reactions were not present in our synthons, leaving the desired ring-expansion process as a viable proposition.

RESULTS AND DISCUSSION

The readily available epoxy-ketone (1) [7] was photolysed in methanol containing 2,5-dimethylhexa-2,4-diene and a small quantity of sodium hydrogencarbonate, using quartz-filtered light; three products were isolated after chromatography over alumina. The major product was the crystalline epoxy-acetal (3) (42%) a known prostaglandin intermediate.[8] The isomeric acetal (4)



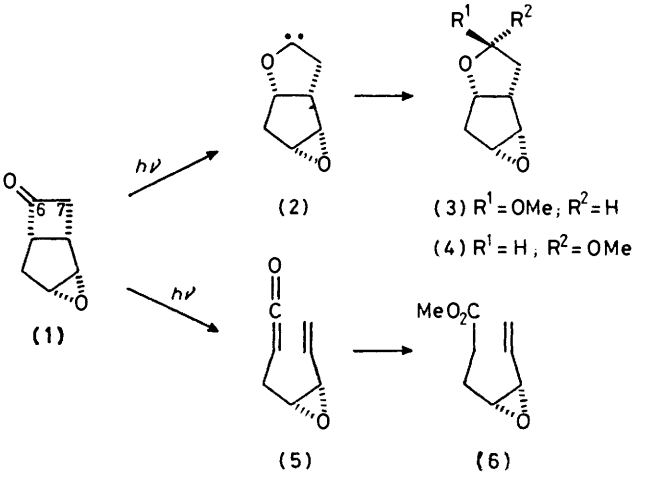
SCHEME 1

was also formed (11%) and could be transformed into (3) using BF_3 in methanol.[9] From large-scale runs a small quantity (≤6%) of the epoxy-ester (6) was also isolated and identified. The acetals (3) and (4) are undoubtedly formed by solvolysis of the intermediate oxacarbene (which may be formed directly from the ketone or *via* an alkyl-acyl diradical). The ester (6) is formed by an unexpected Norrish Type I cleavage of the C^6–C^7 bond, followed by formation and methanolysis of the keten (5) (Scheme 2). No evidence for the formation of the mono-epoxide of cyclopentadiene was found. Omission of the base and/or the diene led to a decreased

yield of (3) and (4). Photolysis through a glass filter led to a slower conversion to products.

The ketone (7) [10] gave a complex mixture of products on photolysis in methanol using a quartz filter. However, on employing all glass apparatus a slow reaction occurred to generate the acetals (12) and (15) (33%) and the alkene (18) (18%). The acetal (12) is a known precursor to prostaglandins.[8] Similarly the dihydroxyketone (8) [10] gave the acetals (13) and (16) (31%) and the alkene (19) (37%). Hydrolysis of (13) and (16) gave the lactol (21), which was converted into prostaglandin $F_{2\alpha}$ by reaction with the appropriate Wittig reagent.[11] Finally the bis(silyloxy)ketone (9) [10] gave the acetals (14) and (17) (35%) and the alkene (20) (34%). Treatment of (14) and (17) with 0.1N methanolic sulphuric acid gave (13) and (16) (73%).

Efforts were made to modify the ratio of the photolysis products to favour the formation of the acetals. However, alteration of the photolysis temperature, the use of triplet sensitisers or quenchers, and the use of a low-energy light source led to the same ratio of products,



SCHEME 2

derived from the competing ring-expansion and cycloelimination pathways. This suggested that both sets of products were formed from a singlet or an unquenchable triplet excited state. From a synthetic viewpoint the production of large quantities of the alkene detracted from the synthetic utility of the photolysis process.

An earlier paper describing the photolysis of (26) noted that alkene (keten) production was markedly repressed on conducting the photolysis in an aqueous medium.[12] Following this tenuous analogy we photolysed the simple bicycloheptanone (10) in aqueous tetrahydrofuran and found that the lactol (22) was formed as the sole high-boiling product in high yield. The lactol (22) was synthesised unambiguously by reduction of the lactone (24) with di-isobutylaluminium hydride. The butylketone (11) formed the lactol (23) (77%) on photolysis in aqueous tetrahydrofuran. A small quantity of a non-polar product was also formed but could not be characterised. Finally, the dihydroxyketone (8) gave the lactol (21) (40%) and the alkene (19) (12%) after photolysis in aqueous acetonitrile and chromatography over silica. A Wittig reaction on the

(7) R^1 = CH(SMe)CH=CHSMe; R^2 = OH (12)

(8) R^1 = CH=CHCH(OH)C_5H_{11}; R^2 = OH (13)

(9) R^1 = CH=CHCH(OSiMe$_2$Bu^t)C_5H_{11}; R^2 = OSiMe$_2$Bu^t (14)

(10) R^1 = R^2 = H

(11) R^1 = Bu^n; R^2 = OH

(15) R^1 = CH(SMe)CH=CHSMe; R^2 = OH (18)

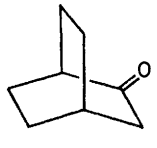
(16) R^1 = CH=CHCH(OH)C_5H_{11}; R^2 = OH (19)

(17) R^1 = CH=CHCH(OSiMe$_2$Bu^t)C_5H_{11}; R^2 = OSiMe$_2$Bu^t (20)

(21) R^1 = CH=CHCH(OH)C_5H_{11}; R^2 = OH

(22) R^1 = R^2 = H (24)

(23) R^1 = Bu^n; R^2 = OH (25)



(26)

crude product from the photolysis suggested that the yield of lactol was *ca.* 70% prior to chromatography.[13]

Thus the yield of the corresponding ring-expanded product on photolysis of a cyclobutanone is greatly enhanced on changing the solvent system from methanol to aqueous tetrahydrofuran or aqueous acetonitrile. To our knowledge, there is only one other report describing

the conversion of a cyclobutanone into a γ-lactol by photolysis in an aqueous medium.[14]

EXPERIMENTAL

M.p.s were determined by the capillary tube method. The Buchi Kugelrohr (bulb-to-bulb) system was used for distillations and the b.p.s reported are oven temperatures at distillation. I.r. spectra were recorded on a Perkin-Elmer 257 spectrometer for neat films unless otherwise stated. N.m.r. spectra were recorded on Varian EM-360 or Perkin-Elmer R-32 spectrometers (CCl_4 or $CDCl_3$ solvent). Column chromatography was performed using alumina type H or silica gel MFC; t.l.c. was accomplished using silica gel G (Merck). Anhydrous magnesium sulphate was used as a drying agent for solutions in organic solvents. Unless otherwise stated light petroleum refers to the fractions boiling at 60—80 °C. The ketones (1),[7] (7),[10] (8),[10] (9),[10] and (11) [10] were prepared as described previously.

Photolysis Procedures.—Method A. The ketone (0.5—2.0 g; 1 equiv.) was dissolved in deoxygenated methanol (80 ml) containing sodium hydrogencarbonate (0.5 g) and 2,5-dimethylhexa-2,4-diene (3 equiv.). The stirred solution was irradiated for a given time using a medium-pressure Hanovia lamp and a quartz filter. The solvent was evaporated and the residue was taken up in diethyl ether (30 ml). The organic phase was washed with water (30 ml) and the aqueous phase was extracted with diethyl ether (3 × 30 ml). The combined organic extracts were dried and evaporated to give the crude product.

Method B. The ketone (0.5—2.0 g) was dissolved in water–tetrahydrofuran (3 : 7)(80 ml). The stirred solution was irradiated for a given time using a medium-pressure Hanovia lamp and a quartz filter. Ether (100 ml) was added and the aqueous phase was separated and washed with ether (3 × 30 ml). The combined ether extracts were dried and evaporated to give the crude product.

Method C. As for method A except all-glass apparatus was employed.

Method D. As for method B except water–acetonitrile (1 : 4) (80 ml) was used in place of aqueous tetrahydrofuran as the solvent system.

Photolysis of the Epoxy-ketone (1).—Method A with an irradiation time of 3.5 h followed by chromatography over alumina gave 6,7-endo-*epoxy*-3-exo-*methoxy*-2-*oxabicyclo*[3.3.0]*octane* (3) (42%), m.p. 52 °C (lit.,[8] m.p. 53—54 °C); δ 5.10 (1 H, dd, *J* 6 and 2 Hz, H-3), 4.65 (1 H, t, *J* 7 Hz, H-1), 3.55—3.45 (2 H, m, H-6 and H-7), 3.25 (3 H, s, OMe), 2.85 (1 H, dddd, *J* 10, 8, 6, and 2 Hz, H-5), and 2.35—1.85 (4 H, m, 2 × H-4 and 2 × H-8) (Found: M^+, 156.078 5. Calc. for $C_8H_{12}O_3$: *M*, 156.078 5): 6,7-endo-*epoxy*-3-endo-*methoxy*-2-*oxabicyclo*[3.3.0]*octane* (4) (11%); $\nu_{max.}$ 735 cm^{-1}; δ 4.95 (1 H, t, *J* 6 Hz, H-3), 4.55 (1 H, t, *J* 7 Hz, H-1), 3.55—3.40 (5 H, m, H-6, H-7, and OMe), 2.85—2.55 (1 H, m, H-5), and 2.35—1.80 (4 H, m, 2 × H-4 and 2 × H-8) (Found: M^+, 156.078 5. $C_8H_{12}O_3$ requires *M*, 156.078 5): and *methyl* 4,5-*epoxyhept*-6-*enoate* (6) (6%); δ 6.0—5.2 (3 H, m, H-6 and 2 × H-7), 3.70 (3 H, s, CO_2Me), 3.40 (1 H, dd, H-5), 3.17 (1 H, m, H-4), 2.50 (2 H, t, 2 × H-2), and 1.8 (2 H, m, 2 × H-3) (Found: C, 61.15; H, 7.8. $C_8H_{12}O_3$ requires C, 61.5; H, 7.75%).

Photolysis of the Bis(methylthio)propenyl Ketone (7).—Method C, with an irradiation time of 16 h, followed by chromatography over silica, eluting with ethyl acetate–light petroleum, gave the 7-endo-*hydroxy*-3-*methoxy*-6-exo-[1′,3′-*bis*(*methylthio*)*prop*-2′-*enyl*]2-*oxabicyclo*[3.2.0]*octanes* (12) and (15) (33%); $\nu_{max.}$ 3 430 cm^{-1}; δ 6.1 (1 H, d, *J* 15 Hz, H-3′), 5.6—4.9 (2 H, m, H-3 and H-2′), 4.6—3.9 (2 H, m, H-1 and H-7), 3.5—2.8 (4 H, m, H-5, H-6, H-1′, and OH), 3.30 (3 H, s, OMe), 2.75—1.5 (4 H, m, 2 × H-4 and 2 × H-8), 2.2 (3 H, s, SMe), and 2.0 (3 H, s, SMe) (Found: M^+, 290.100 8. $C_{13}H_{22}O_3S_2$ requires *M*. 290.101 0): and trans-4-*hydroxy*-3-[1′,3′-*bis*(*methylthio*)*prop*-2′-*enyl*]*cyclopent*-1-*ene* (18) (18%); $\nu_{max.}$ 3 400 cm^{-1}; δ 6.1 (1 H, dd, *J* 15 and 2 Hz, H-3′), 5.70 (2 H, m, H-1 and H-2), 5.45 (1 H, dd, *J* 15 and 2 Hz, H-2′), 4.3 (1 H, m, H-4), 3.3—2.3 (5 H, m, H-3, 1 × H-5, H-1′, and OH), 2.25 (3 H, s, SMe), and 2.0 (3 H, s, SMe) (Found: M^+, 216.064 1. $C_{10}H_{16}OS_2$ requires *M*, 216.064 2).

Photolysis of the Dihydroxyketone (8).—Method A, irradiation time 2 h, with chromatography of the crude product over silica using ethyl acetate–light petroleum as eluant gave the 7-endo-*hydroxy*-6-exo-(3′-*hydroxyoct*-1′-*enyl*)-3-*methoxy*-2-*oxabicyclo*[3.3.0]*octanes* (13) and (16) (31%) [Found: M^+, 253.180 1. $C_{16}H_{28}O_4$ requires (*M* − OMe), 253.180 2] and trans-4-*hydroxy*-3-(3′-*hydroxyoct*-1′-*enyl*)*cyclopent*-1-*ene* (19) (37%); $\nu_{max.}$ 3 350 cm^{-1}; δ 5.55 (4 H, m, H-1, H-2, H-1′, and H-2′), 4.10 (2 H, m, H-4 and H-3′), 3.15 (1 H, m, H-3), 3.00 (2 H, br s, 2 × OH), 2.65—2.05 (2 H, m, 2 × H-5), 1.3 (8 H, m, 4 × CH_2), and 0.9 (3 H, s, Me) [Found: M^+, 192.151 2. $C_{13}H_{22}O_2$ requires (*M* − H_2O), 192.151 3].

A mixture of the acetals (13) and (16) (0.28 g) was dissolved in acetonitrile–water (2 : 1) (10 ml) and treated with 0.5N HCl (4 ml) for 3 h. Water (20 ml) was added, followed by extraction with ether (6 × 30 ml). The combined ether extracts were dried and evaporated to give the lactol (21) (100%), identical (n.m.r., t.l.c.) with an authentic sample.

Method D, irradiation time 4 h, with chromatography of the crude product over silica, gave the lactol [3] (21) (40%) and the *alkene* (19) (12%).

Photolysis of the Bis(silyloxy)ketone (9).—Method A, involving an irradiation time of 4 h, followed by chromatography over alumina using ethyl acetate–light petroleum, gave the 7-endo-(*t-butyldimethylsilyloxy*)-6-exo-[3′-(*t-butyldimethylsilyloxy*)*oct*-1′-*enyl*]-3-*methoxy*-2-*oxabicyclo*-[3.3.0]*octanes* (14) and (17) (35%); δ 5.45 (2 H, m, H-1′ and H-2′), 5.1 (1 H, m, H-3), 4.6—3.65 (3 H, m, H-1, H-7, and H-3′), 3.25 (3 H, s, OMe), 2.8—1.66 (6 H, m, 2 × H-4, H-5, H-6, and 2 × H-8), 1.25 (8 H, m, 4 × CH_2), 0.85 (21 H, m, 3 × H-8 and 2 × CMe_3), and 0.05 (12 H, s, 2 × $SiMe_2$) [Found: M^+, 481.353 0. $C_{28}H_{56}O_4Si_2$ requires (*M* − OMe), 481.353 0] and the alkene (20) (34%) (Found: C, 67.4, H, 11.8. $C_{25}H_{50}O_2Si_2$ requires C, 67.5; H, 11.4%). The acetals (14) and (17) (256 mg) were treated with 0.1N methanolic sulphuric acid (5.0 ml) for 20 h. at −20 °C. The solution was then poured into aqueous sodium carbonate and extracted with chloroform. The dried extracts were evaporated to give an oil which was chromatographed over silica (ethyl acetate–light petroleum as eluant) to give the acetals (13) and (16) (73%).

Photolysis of Bicyclo[3.2.0]*heptan*-6-*one* (10).—Method B and an irradiation time of 2 h gave pure *lactol* (22) (75%); $\nu_{max.}$ 3 400 cm^{-1}; δ 5.5 (1 H, d, *J* 5 Hz, H-3), 4.95—4.3 (2 H, m, H-1 and OH), and 2.7—0.9 (9 H, m, H-5 and 4 × CH_2) [Found: M^+, 111.081 2. $C_7H_{12}O_2$ requires (*M* − OH), 111.081 0]. The lactol (22) (0.3 g) in diethyl ether (15 ml) was treated with Jones reagent at 0 °C for 3 h to give the *lactone* (24) (50%); δ 5.0 (1 H, t, H-1), 2.9—2.2 (3 H, m, H-5 and 2 × H-4), and 2.05—1.15 (6 H, m,

3 × CH_2) (Found: M^+, 126.068 0. $C_7H_{10}O_2$ requires M, 126.068 0). Reduction of the lactone (24) using di-isobutyl aluminium hydride in the standard fashion gave the lactol (22) (85%).

Photolysis of the Butylhydroxyketone (11).—Method B, with an irradiation time of 4 h gave, as the only isolable product (after chromatography over silica), 6-exo-*butyl*-3,7-endo-*dihydroxy*-2-*oxabicyclo*[3.3.0]*octane* (23) (77%); $\nu_{max.}$ 3 360 cm^{-1}; δ 5.60—5.45 (1 H, m, H-3), 4.60 (1 H, m, H-7), 4.0—3.5 (3 H, m, H-1 and 2 × OH), 2.5—1.5 (6 H, 2 × H-4, H-5, H-6, and 2 × H-8), 1.25 (6 H, br s, 3 × CH_2), and 0.85 (3 H, t, Me) [Found: M^+, 182.130 5. $C_{11}H_{20}O_3$ requires (M − H_2O), 182.130 6]. The lactol (23) was oxidised with Collins reagent to give the *lactone* (25) (72%); δ 5.0 (1 H, m, H-1), 4.1 (1 H, m, H-7), 3.3 (1 H, br s, OH), 2.9—2.4 (2 H, m, 2 × H-4), 2.2—1.7 (2 H, m, H-5 and H-6), 1.48 (8 H, m, 4 × CH_2), and 0.93 (3 H, s, Me) (Found: M^+, 198.126 1. $C_{11}H_{18}O_3$ requires M, 198.125 5). Treatment of the lactone (25) with di-isobutyl aluminium hydride under standard conditions gave the lactol (23) (85%).

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REFERENCES

[1] D. R. Morton and N. J. Turro, *Adv. Photochem.*, 1974, **9**, 138.
[2] Cyclopentanones having particular substitution patterns have been shown to undergo ring-expansion; P. Yates and R. O. Loutfy, *Accounts Chem. Res.*, 1975, **8**, 209; P. Yates and L. Kilmurry, *Tetrahedron Letters*, 1964, 1739.
[3] Preliminary communications: N. M. Crossland, S. M. Roberts, and R. F. Newton, *J.C.S. Chem. Comm.*, 1978, 661; R. F. Newton, C. C. Howard, D. P. Reynolds, A. H. Wadsworth, N. M. Crossland, and S. M. Roberts, *ibid.*, 1978, 662; N. M. Crossland, D. R. Kelly, S. M. Roberts, D. P. Reynolds, and R. F. Newton, *ibid.*, 1979, 681.
[4] C. C. Howard, R. F. Newton, D. P. Reynolds, A. H. Wadsworth, D. R. Kelly, and S. M. Roberts, *J.C.S. Perkin I*, 1980, 852.
[5] G. Jones and S. A. Zalk, *Tetrahedron Letters*, 1973, 4095; see also H. U. Hostettler, *ibid.*, 1965, 687.
[6] G. Jones and L. P. McDonnell, *J. Amer. Chem. Soc.*, 1976, **98**, 6203.
[7] S. M. Ali, N. M. Crossland, T. V. Lee, S. M. Roberts, and R. F. Newton, *J.C.S. Perkin I*, 1979, 122.
[8] E. J. Corey and R. Noyori, *Tetrahedron Letters*, 1970, 311.
[9] E. J. Corey, K. C. Nicholaou, and D. J. Beames, *Tetrahedron Letters*, 1974, 2439.
[10] R. J. Cave, C. C. Howard, G. Klinkert, R. F. Newton, D. P. Reynolds, A. H. Wadsworth, and S. M. Roberts, *J.C.S. Perkin I*, 1979, 2954.
[11] See T. V. Lee, S. M. Roberts, M. J. Dimsdale, R. F. Newton, D. K. Rainey, and C. F. Webb, *J.C.S. Perkin I*, 1978, 1176.
[12] S. C. Critch and A. G. Fallis, *Canad. J. Chem.*, 1977, **55**, 2845.
[13] R. F. Newton, D. P. Reynolds, N. M. Crossland, D. R. Kelly, and S. M. Roberts, *J.C.S. Chem. Comm.*, 1979, 683.
[14] D. R. Morton, E. Lee-Ruff, R. M. Southam, and N. J. Turro, *J. Amer. Chem. Soc.* 1970, **92**, 4349.