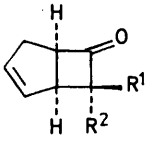
Some Stereocontrolled Reactions of Bicyclo[3.2.0]heptan-6-ones and 2-Oxabicyclo[3.3.0]octan-3-ones

By **S. Mubarik Ali, Noelle M. Crossland, Thomas V. Lee,** and **Stanley M. Roberts,*** The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT
Roger F. Newton,* External Projects Department, Allen and Hanburys Research Ltd., Ware, Hertfordshire SG12 0DJ

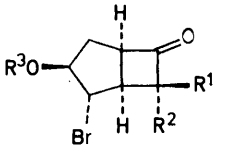
2-Oxabicyclo[3.3.0]oct-6-en-3-one reacts with bromine through the formation of *exo*- and *endo*-bromonium ions. The regioselectivity of the reactions of bromonium ions derived from 4-bromo-4-methyl-2-oxabicyclo[3.3.0]oct-6-en-3-ones hinges on the configurations of the substituents at C-4. These bromonium ions are attacked by nucleophiles at C-7, the carbon centre more distant from the lactone ring, with high selectivity. Similarly, acid catalysed ring cleavages of epoxides derived from bicyclo[3.2.0]hept-2-en-6-one and 2-oxabicyclo[3.3.0]oct-6-en-3-ones take place with marked selectivity. Conformational preferences of the adjacent ketone or lactone ring in the intermediate bromonium ions and protonated epoxides are invoked to explain the various selectivities observed.

FULL exploitation of bicyclo[3.2.0]heptan-6-ones and the related 2-oxabicyclo[3.3.0]octan-3-ones in organic synthesis necessitates an appreciation and the utilization of the steric factors influencing attack by reagents at receptive sites in the five-membered ring (*e.g.* an olefinic unit).

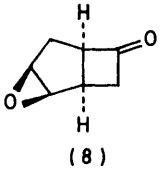
We wish to show that the regioselectivity of attack on the carbocyclic ring and the preferred conformation of intermediates are determined by the size of, and the substitution pattern in, the adjacent carbonyl-containing ring.



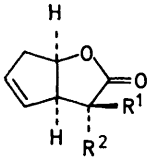
(1) $R^1 = R^2 = H$
(3) $R^1 = Br$, $R^2 = Me$
(4) $R^1 = Me$, $R^2 = Br$



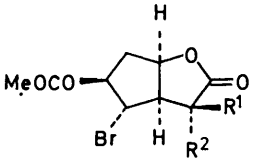
(2) $R^1 = R^2 = H$, $R^3 = COMe$
(5) $R^1 = R^2 = H$, $R^3 = Me$
(6) $R^1 = Br$, $R^2 = R^3 = Me$
(7) $R^1 = R^3 = Me$, $R^2 = Br$
(9) $R^1 = R^2 = R^3 = H$



(8)

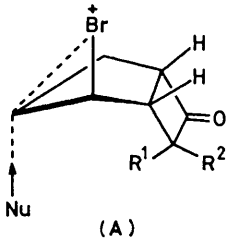


(10) $R^1 = R^2 = H$
(20) $R^1 = Br$, $R^2 = Me$
(23) $R^1 = Me$, $R^2 = Br$

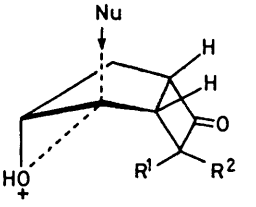


(11) $R^1 = R^2 = H$
(21) $R^1 = Br$, $R^2 = Me$
(25) $R^1 = Me$, $R^2 = Br$

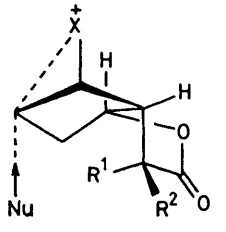
Bicyclo[3.2.0]hept-2-en-6-one (1) reacted with bromine in acetic acid to give the *exo*-bromonium ion and thence the 3-*endo*-acetoxy-2-*exo*-bromoheptan-6-one (2).[1] Similarly the bicycloheptenones (1), (3), and (4)



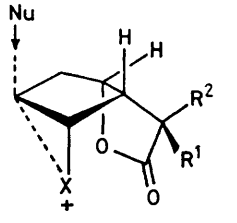
(A)



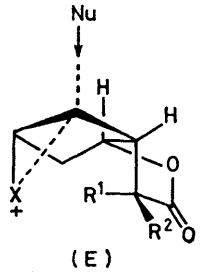
(B)



(C)



(D)



(E)

X = Br, OH; Nu = nucleophile

gave the bromo-ethers (5)—(7) respectively on treatment with bromine in methanol. Obviously formation of the *endo*-bromonium ion is a sterically prohibited process.

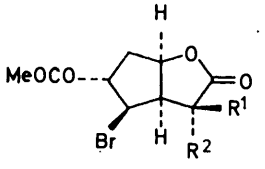
The epoxide (8), formed quantitatively from the bromohydrin (9) by the action of methoxide ion, was readily ring opened by HBr in acetic acid with the nucleophile attacking C-2 with high selectivity (>80%) furnishing the bromo-acetate (2). Ring opening of the

above bromonium ions and the protonated epoxide took place through the highly favoured transition states (A) and (B) with the five-membered ring in an envelope conformation [1] and with the incipient 2-*exo*- and 3-*endo*-substituents *trans*-oriented and co-axially disposed.[2]

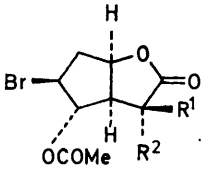
In complete contrast to the corresponding reaction of ketone (1) 2-oxabicyclo[3.3.0]oct-6-en-3-one (10) [3] reacted with bromine non-selectively. For example bromination of the lactone (10) in acetic acid solution gave a three component mixture; the constituents were separated by preparative t.l.c. and identified as the bromo-acetates (11) (36%), (12) (45%), and (13) (9%).

It has previously been shown that in brominations involving *N*-bromoacetamide (NBA) in protic solvents, bromonium ion formation is reversible. and attack by the nucleophile is slow and defines specificity.[4] Formation of the bromo-acetate (11) from the intermediate *exo*-bromonium ion involved selective attack by acetic acid at C-7. Of the possible arrangements for this ring-opening in the more flexible bicyclo-octanone system, we favour the transition state (C) with the cyclopentane ring in a half-chair conformation so that eclipsing of the four substituents on this ring with neighbouring atoms is avoided. The lactone (12) was formed from the *endo*-bromonium ion through the transition state (D): in this transition state non-bonded interactions are minimised. The minor product (13) was also formed from the *endo*-bromonium ion, but through the transition state (E) which has an unfavourable transannular interaction between the bromine atom and *endo*-4-H.

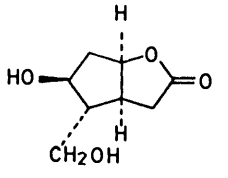
In view of the non-selectivity of bromination of the lactone (10), the high selectivity of the Prins reaction on the same lactone (10) [5] is quite remarkable. The selective formation of the *exo*-bromonium ion and consequently the bromohydrin (15) on bromination of the



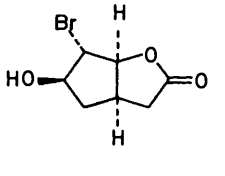
(12) $R^1 = R^2 = H$
(22) $R^1 = Br$, $R^2 = Me$
(24) $R^1 = Me$, $R^2 = Br$



(13) $R^1 = R^2 = H$
(30) $R^1 = Me$, $R^2 = Br$
(31) $R^1 = Br$, $R^2 = Me$



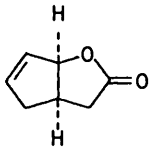
(14)



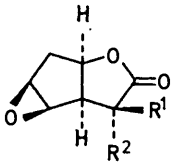
(15)

lactone (16) in an aqueous medium [6] may be due to difficulty in the formation of the *endo*-bromonium ion.

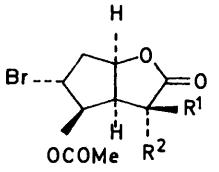
The known *endo*-epoxy-lactone (17) [7] was attacked by HBr in acetic acid to give equal amounts of the bromo-acetates (11) [through transition state (E)] and (18) [through transition state (D)]. Analogous non-selective



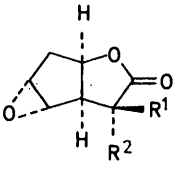
(16)



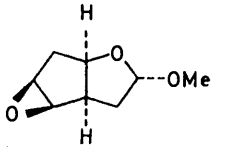
(17) $R^1 = R^2 = H$
(26) $R^1 = Me$ $R^2 = Br$



(18) $R^1 = R^2 = H$
(27) $R^1 = Me$, $R^2 = Br$



(28) $R^1 = CH_3$, $R^2 = Br$
(29) $R^1 = Br$, $R^2 = Me$



(19)

opening of the corresponding acetal (19) proved a serious flaw in an otherwise useful route to prostaglandins.[8]

Treatment of the 4-*endo*-bromo-lactone (20) with (NBA) in acetic acid yielded the 4-*endo*,6-*exo*-dibromo-lactone (21) (80%) almost exclusively, through attack on the *exo*-bromonium ion by acetic acid at C-7 involving the transition state (C). The minor product was the bromo-ester (22) (11%) derived from the *endo*-bromonium ion. The formation of only a relatively small amount of product from the *endo*-bromonium ion may be due to the transition states (D) and (E) being disfavoured. In transition state (D) the carbonyl group and the equatorial bromine atom at C-4 are closely aligned, an unfavourable situation,[2,9] while in the transition state (E) a very severe interaction between the two bromine atoms is encountered. The experimental result suggests that from the *endo*-bromonium ion, transition state (D) is the lower energy pathway.

In direct contrast to the last example treatment of the 4-*exo*-bromo-lactone (23) with NBA in acetic acid gave the 4-*exo*,6-*endo*-dibromo-lactone (24) (80%) through ready formation of the *endo*-bromonium ion and participation of the transition state (D). Note that the bromine atom is pseudoaxial in this transition state. Only a small amount (10%) of the bromo-acetate (25) formed from the *exo*-bromonium ion was detected. Obviously, the transition states (C) and (E) are unfavourable; both have the 4-Br and C=O dipoles aligned and the latter suffers from the interaction of the *endo*-substituents.

In a complementary fashion, the 4-*exo*-bromo-6,7-*endo*-epoxy-lactone (26) on treatment with HBr in acetic acid gave a bromohydrin which on acetylation furnished the bromoacetate (27). The protonated epoxide was opened through transition state (D). Only a very small amount of the bromoacetate (25) was formed through the less favourable transition state (E).

As expected the *exo*-epoxylactones (28) and (29) were ring opened using HBr in acetic acid to give the bromoacetates (30) and (31) respectively through the transition state (C).

To summarise, nucleophilic attack on the *exo*-bromonium ions and the protonated *exo*-epoxides of the 2-oxabicyclo[3.3.0]oct-6-en-3-ones (10), (20), and (23), and on the *exo*-bromonium ion of bicyclo[3.2.0]hept-2-en-6-one (1) takes place at the carbon atom more distant from the bridgehead position. Nucleophilic attack on protonated 2,3-*endo*-epoxybicyclo[3.2.0]-heptan-6-one (8) takes place predominantly at C-2.

The *endo*-bromonium ions and protonated *endo*-epoxides derived from 2-oxabicyclo[3.3.0]oct-6-en-3-ones (10), (20), and (23) are attacked by nucleophiles at C-6 and -7. The regioselectivity of the nucleophilic attack is dictated by the nature and the configuration of the substituents at C-4. These substituents exert their influence by raising the energy of some of the possible transition states due to unfavourable transannular steric interactions or by the unfavourable alignment of dipoles. Utilizing the results and mechanistic rationale described above, routes to some desired synthetic goals have been devised and explored. These results will be communicated in due course.

Configurational assignments of the new compounds described above were accomplished by analysis of the ^{1}H n.m.r. spectra using double irradiation techniques where necessary.*

EXPERIMENTAL

The Buchi Kügelrohr (bulb-to-bulb) system was used for distillation and the b.p.s reported are oven temperatures at distillation. M.p.s were determined by the capillary tube method. N.m.r. spectra were recorded on a Varian EM-360 or Perkin-Elmer R-32 spectrometer (CCl_4 or $CDCl_3$ solvent). I.r. spectra were recorded on a Perkin-Elmer 257 spectrometer for neat films unless otherwise stated. Column chromatography was performed using silica gel MFC; t.l.c. was accomplished using silica gel G (Merck). Anhydrous sodium sulphate was used as a drying agent for solutions in organic solvents. Unless otherwise stated light petroleum refers to the fraction boiling at 60—80°.

Reaction of the Bicyclic Ketones (3) *and* (4) *with NBA in Methanol.*—To a solution of 7-*exo*-bromo-7-*endo*-methylbicyclo[3.2.0]hept-2-en-6-one (4) [10] (2.0 g) in methanol (20 ml) was added NBA (1.6 g). After 15 h at room temperature the mixture was diluted with water (60 ml) and extracted with ether (4 × 15 ml). The combined ether extracts were washed with water (3 × 15 ml), dried, and evaporated to yield 2-exo,7-exo-*dibromo*-3-endo-*methoxy*-7-endo-*methylbicyclo*[3.2.0]*heptan*-6-*one* (7) as an oil (2.6 g, 85%), b.p. 100—104° at 0.03 mmHg; $\nu_{max.}$ 1 780 cm^{-1}; δ 4.53 (1 H, s, H-2), 4.1 (2 H, m, H-3 and -5), 3.6 (1 H, d, *J* 8.0 Hz, H-1), 2.3 (2 H, m, 2 × H-4), and 1.8 (3 H, s, Me) (Found: *M*$^+$, 309.920 3. $C_9H_{12}Br_2O_2$ requires *M*, 309.920 4).

Similarly, reaction of 7-*endo*-bromo-7-*exo*-methylbicyclo-[3.2.0]hept-2-en-6-one (3) [10] with NBA in methanol yielded 2-exo,7-endo-*dibromo*-3-endo-*methoxy*-7-exo-*methylbicyclo*-[3.2.0]*heptan*-6-*one* (6) as cubes (85%), m.p. 73—74° (chloroform–petroleum); $\nu_{max.}$ 1 780 cm^{-1}; δ 4.55 (1 H, s, H-2), 4.0 (2 H, m, H-3 and -5), 3.3 (3 H, s, OCH_3), 3.25 (2 H, m, 2 × H-4), and 1.9 (3 H, s, Me) (Found: C, 34.3; H, 3.9. $C_9H_{12}Br_2O_2$ requires C, 34.6; H, 3.8%).

Reaction of 2-*Oxabicyclo*[3.3.0]*oct*-6-*en*-3-*one* (10) *with NBA in Acetic Acid.*—To the lactone (10) [3] (1.0 g) in glacial acetic acid (20 ml) was added NBA (1.4 g). After 15 h at room temperature the mixture was worked up as described above. The three bicyclic lactones (11)—(13) were obtained in a 4 : 5 : 1 ratio. Separation was achieved by column chromatography followed by t.l.c. to give (i) 7-endo-*acetoxy*-6-exo-*bromo*-2-*oxabicyclo*[3.3.0]*octan*-3-*one* (11) (0.75 g, 36%), $\nu_{max.}$ 2 960, 1 770, and 1 740 cm^{-1} (Found: C, 41.0; H, 4.4. $C_9H_{11}BrO_4$ requires C, 41.1; H, 4.2%), (ii) 7-exo-*acetoxy*-6-endo-*bromo*-2-*oxabicyclo*[3.3.0]*octan*-3-*one* (12) (0.95 g, 45%), $\nu_{max.}$ 1 780, 1 750, and 1 230 cm^{-1} (Found: *M*$^+$, 261.984 1. $C_9H_{11}BrO_4$ requires *M*, 261.984 2), and (iii) 6-exo-*acetoxy*-7-endo-*bromo*-2-*oxabicyclo*[3.3.0]*octan*-3-*one* (13) (0.19 g, 9%), b.p. 90—95° at 0.05 mmHg, $\nu_{max.}$ 1 770, 1 420, 1 240, and 1 040 cm^{-1} (Found: *M*$^+$, 261.984 1. $C_9H_{11}BrO_4$ requires *M*, 261.984 2).

Treatment of 4-endo-*Bromo*-4-exo-*methyl*-2-*oxabicyclo*-[3.3.0]*oct*-6-*en*-3-*one* (20) *with NBA in Acetic Acid.*—To a solution of the lactone (20) [10] (0.43 g) in glacial acetic acid (5 ml) was added NBA (0.4 g). After 15 h at room temperature the mixture was worked up as described above. The residue, a mixture of the bicyclic lactones (21) and (22) (7 : 1), was purified by column chromatography to give 7-endo-*acetoxy*-4-endo,6-exo-*dibromo*-4-exo-*methyl*-2-*oxabicyclo*[3.3.0]*octan*-3-*one* (21) as an oil (0.56 g, 80%), b.p. 150° at 0.03 mmHg, $\nu_{max.}$ 1 790 and 1 750 cm^{-1} (Found: C, 34.0; H, 3.5. $C_{10}H_{12}Br_2O_4$ requires C, 33.7; H, 3.4%).

Treatment of 4-exo-*Bromo*-4-endo-*methyl*-2-*oxabicyclo*-[3.3.0]*octan*-3-*one* (23) *with NBA in Acetic Acid.*—To a solution of the lactone (23) [10] (0.43 g) in glacial acetic acid (5 ml) was added NBA (0.4 g). After 15 h at room temperature the mixture was worked up as above. The residue, a mixture of the bicyclic lactones (25) and (24) (1 : 8) was chromatographed. 7-exo-*Acetoxy*-4-exo,6-endo-*dibromo*-4-endo-*methyl*-2-*oxabicyclo*[3.3.0]*octan*-3-*one* (24) was obtained as an oil (0.56 g, 80%), b.p. 160° at 0.005 mmHg, $\nu_{max.}$ 1 785 and 1 740 cm^{-1} (Found: C, 33.8; H, 3.5. $C_{10}H_{12}Br_2O_4$ requires C, 33.7; H, 3.4%).

2,3-endo-*Epoxybicyclo*[3.2.0]*heptan*-6-*one* (8).—To a solution of 2-exo-*bromo*-3-endo-*hydroxybicyclo*[3.2.0]*heptan*-6-*one* (9) [1] (1.0 g) in methanol (15 ml) was added sodium methoxide (0.5 g) and the mixture was stirred at 0° for 15 min followed by 45 min at room temperature. Water (50 ml) was added and the suspension was extracted with chloroform (3 × 50 ml). The combined organic extracts were dried, evaporated, and distilled to yield the required *epoxy-ketone* (8) as an oil (0.60 g, 98%), b.p. 65° at 0.005 mmHg, $\nu_{max.}$ 2 950, 1 780, and 845 cm^{-1}; δ 3.6 (m, 3 H, H-2, -3, and -5), 2.9 (m, 3 H, H-1 and 2 × H-7), 2.35 (1 H, d,

* ^{1}H N.m.r. chemical shift and coupling constant data are available in Supplementary Publication No. SUP 22344 (3 pp). For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1977, Index issue.

J 14 Hz, *endo*-4-H), 1.85 (1 H, dd, *J* 14 and 9 Hz, *exo*-4-H) (Found: M^+, 124.052 4. $C_7H_8O_2$ requires *M*, 124.052 4).

Acid Catalysed Epoxy-ring Opening of Bicyclic Ketone (8) *and Bicyclic Lactones* (17), (26), (28), *and* (29).—To a solution of the appropriate epoxy-ketone or epoxy-lactone (0.005 mol) in glacial acetic acid (5 ml) was added hydrobromic acid (5 ml; 49% in acetic acid). After 2 h at room temperature the solution was evaporated under reduced pressure. The products were purified by column chromatography and t.l.c.

(a) 3-endo-*Acetoxy*-2-exo-*bromobicyclo*[3.2.0]*heptan*-6-*one* (2). The *endo*-epoxy-ketone (8) was treated with HBr as described above except that the mixture was neutralised ($NaHCO_3$) and the organic material was extracted into chloroform. The chloroform extract was dried and evaporated to give an oil (95%). Purification by column chromatography ($CHCl_3$) yielded the *acetoxy-ketone* (2) (80%). (N.m.r. and i.r. spectra were identical with the authentic sample.)

(b) 6,7-*endo*-Epoxy-2-oxabicyclo[3.3.0]octan-3-one (17)[7] on treatment with hydrobromic acid yielded a mixture of two compounds. Separation was achieved by h.p.l.c. by injecting a 10 μl sample of the mixture onto a μ-Porasil column and employing iso-octane–ethyl acetate (85 : 15) as eluant at a rate of 1 ml min^{-1}. This gave (i) 7-endo-*acetoxy*-6-exo-*bromo*-2-*oxabicyclo*[3.3.0]*octan*-3-*one* (50%) (11) and (ii) 6-endo-*acetoxy*-7-exo-*bromo*-2-*oxabicyclo*[3.3.0]-*octan*-3-*one* (18) as a colourless oil (50%), $\nu_{max.}$ 1 785, 1 740, 1 280, and 1 240 cm^{-1} (Found: M^+, 261.984 1. Calc. for $C_9H_{11}BrO_4$: *M*, 261,984 2).

(c) 6-endo-*Acetoxy*-4-exo,7-exo-*dibromo*-4-endo-*methyl*-2-*oxabicyclo*[3.3.0]*octan*-3-*one* (27). The *endo*-epoxy-lactone (26)[10] on treatment with hydrobromic acid, followed by acetylation of the bromohydrin so formed yielded the *acetoxy-lactone* (27) as cubes (85%), m.p. 154—155 °C; $\nu_{max.}$ (Nujol) 1 780 and 1 750 cm^{-1} (Found: C, 33.3; H, 3.3. $C_{10}H_{12}Br_2O_4$ requires C, 33.6; H, 3.4%).

(d) 6,7-exo-Epoxy-2-oxabicyclo[3.3.0]octan-3-one (29)[7] on treatment with hydrobromic acid yielded 6-exo-*acetoxy*-7-endo-*bromo*-2-*oxabicyclo*[3.3.0]*octan*-3-*one* (31) as an oil (95%).

(e) 6-exo-*Acetoxy*-4-exo,7-endo-*dibromo*-4-endo-*methyl*-2-*oxabicyclo*[3.3.0]*octan*-3-*one* (30). Hydrobromic acid treatment of the *exo*-epoxy-lactone (28)[11] yielded a bromohydrin as needles (85%), m.p. 127—128° (from chloroform), $\nu_{max.}$ 3 240 and 1 775 cm^{-1} (Found: C, 30.3; H, 3.1. $C_8H_{10}Br_2O_3$ requires C, 30.5; H, 3.2%). Acetylation yielded the *lactone* (30) as prisms (92%), m.p. 111—112°, $\nu_{max.}$ (Nujol) 1 780 and 1750 cm^{-1} (Found: C, 33.5; H, 3.4. $C_{10}H_{12}Br_2O_4$ requires C, 33.7; H, 3.3%).

We thank the S.R.C. and Allen and Hanburys Research for CASE studentships (N. M. C., T. V. L.) and the S.R.C. for a post-doctoral fellowship (S. M. A.). We are grateful to Allen and Hanburys Research for generous gifts of chemicals and to Mr. R. Thomson for separations performed on h.p.l.c. equipment.

[8/136 *Received*, 27*th January*, 1978]

REFERENCES

[1] Z. Grudzinski and S. M. Roberts, *J.C.S. Perkin I*, 1975, 1767.
[2] E. Eliel, 'The Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962.
[3] P. A. Grieco, *J. Org. Chem.*, 1972, **37**, 2363.
[4] C. Anselmi, G. Berti, G. Catelani, L. Lecce, and L. Monti, *Tetrahedron Letters*, 1977, 2274.
[5] I. Tomoskozi, L. Gruber, G. Kovacs, I. Szekely, and V. Simonidesz, *Tetrahedron Letters*, 1976, 4639.
[6] S. Ranganathan, D. Ranganathan, and A. K. Mehrotra, *Tetrahedron Letters*, 1975, 1215.
[7] E. J. Corey and R. Noyori, *Tetrahedron Letters*, 1970, 311.
[8] E. J. Corey, K. C. Nicolaou, and D. J. Beames, *Tetrahedron Letters*, 1974, 2439.
[9] See G. Jones and L. P. McDonnell, *J. Amer. Chem. Soc.*, 1976, **98**, 6205 for a discussion on the conformational preferences of the related 7-halogenobicyclo[3.2.0]heptan-6-ones.
[10] S. M. Ali and S. M. Roberts, *J.C.S. Perkin I*, 1976, 1934 and references therein.
[11] S. M. Ali, C. B. Chapleo, and S. M. Roberts, following paper.