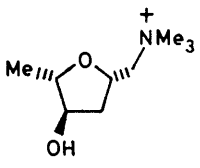
Oxyallyls in Synthesis. Preparation of Analogues of Muscarine and α-Multistriatin

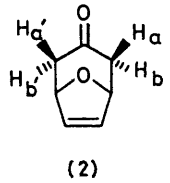
By **Antony P. Cowling, John Mann,* and Attique A. Usmani,** Department of Chemistry, Reading University, Whiteknights, Reading RG6 2AD

Oxyallyls react readily with furans, and we have used the cycloadducts formed in the syntheses of structural analogues of the natural products muscarine and α-multistriatin. In addition we give details of a new method of forming oxyallyls from monobromo-ketones.

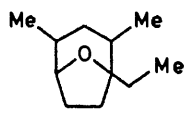
In a previous paper [1] we described the preparation of several biologically active analogues of cocaine, as an illustration of the synthetic utility of oxyallyls. We discovered that furans readily undergo cycloaddition to



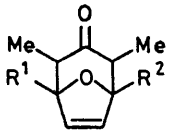
(1)



(2)



(3)



(4)

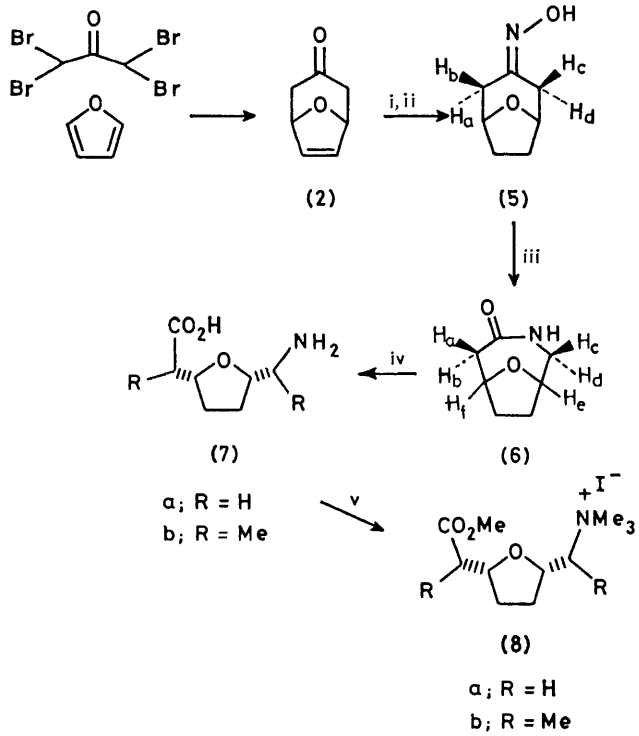
a; R^1 = H, R^2 = Me

b; R^1 = H, R^2 = Et

c; R^1 = R^2 = Me

give cycloadducts in high yield. These offered promise as starting materials for the construction of natural products and structurally related compounds. Thus products resembling (+)-muscarine (1), a cholinergic agent present in the mushroom *Amanita muscaria*, might be obtained from the bicyclo-octene (2). Also, analogues of α-multistriatin (3), one of the components of the aggregation pheromone of the European elm-bark beetle *Scolytus scolytus*,[2] might be derived from the bicyclo-octenes (4). The attainment of these synthetic goals is the subject of this paper.

The cycloadduct (2) was prepared from 1,1,3,3-tetrabromopropanone and furan in the presence of zinc dust and triethyl borate,[3] followed by rapid debromination (zinc dust at −60 °C) of the initial dibromo-cycloadduct (see the Scheme). Yields were rather disappointing (25—30%), but the alternative method of Noyori [4] using the expensive reagent nona-carbonyldi-iron produced (at least in our hands) little improvement. Compound (2) is very unstable; it darkens even at −15 °C under an atmosphere of nitrogen and was normally used without further purification. However, a pure sample was obtained for the purposes of characterisation and the n.m.r. spectrum was rather interesting because it exhibited long-range coupling of *ca.* 1 Hz for $J_{a'b} = J_{a'b}$. We elected to remove the double bond (10% palladium-on-charcoal in methanol), thus avoiding the presence of an additional chiral centre, but also with the knowledge that the hydroxy-group of muscarine appears not to be essential for biological activity. The crystalline oxime (5) was then prepared by standard methods. Several procedures for effecting the Beckman rearrangement of the oxime (5) into compound (6) were evaluated and the best results were obtained with a 10 : 1 mixture of methanesulphonic acid



(2) (5) (7) (6)

a; R = H

b; R = Me

(8)

a; R = H

b; R = Me

Scheme i, 10% Pd–C; ii, NH_2OH·HCl; iii, P_2O_5–$MeSO_3H$; iv, 12% HCl; v, MeI–K_2CO_3

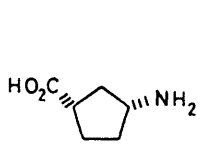
and phosphorus pentaoxide (60%). Hydrolysis of the lactam (6) yielded the amino-acid (7a) which was exhaustively methylated to provide the analogue (8a). As well as the obvious structural relationship with muscarine, these compounds have some features in common with many of the γ-aminobutyric acid (GABA) analogues that have been prepared in the past few years

[*e.g.* compound (9) and see ref. 5]. In the event, biological tests on compounds (7a) and (8a) proved disappointing; they had no muscarinic, or analgetic activity, and were not GABA antagonists. We also prepared the analogues (7b) and (8b) *via* a similar sequence of reactions, but commencing with the cycloadduct obtained from 2,4-dibromopentan-3-one and furan. These, too, were devoid of biological activity. However, the route to disubstituted tetrahydrofurans outlined above is simple and economical and may have some general utility.

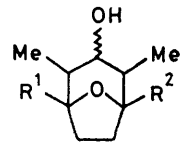
Somewhat better biological results were obtained with the α-multistriatin analogues obtained from the cycloadducts of type (4). These were prepared from the appropriate furans and oxyallyls derived from 2,4-dibromopentan-3-one using sodium iodide and copper powder,[1] or from 2-bromopentan-3-one using silver tetrafluoroborate and triethylamine.[6] This latter, new method deserves some further comment.

We have always thought it desirable to prepare oxyallyls from monobromo-ketones, since there are a number of excellent methods for preparing these that do not require the use of liquid bromine. For example, the method of Macomber and Bauer which employs cupric bromide,[7] and the method for benzyl alkyl ketones using *N*-bromosuccinimide. Initially, we hoped to prepare the oxyallyls merely using base and the appropriate monobromo-ketones. A number of bases were tried including triethylamine, pyridine, and 2,6-lutidine, but although cycloadducts were obtained in some instances, the yields were low or the reactions were irreproducible (compare the recent report in ref. 8). The only exceptions involved the monobromo-ketones derived from benzyl alkyl ketones, from which cycloadducts could be obtained using furan–acetonitrile mixtures in conjunction with triethylamine (1 ml per 10 mmol of ketone). The yields were good (60—70%), but lower stereoselectivity was observed (see the Table). In the presence of silver tetrafluoroborate (but not silver trifluoroacetate or silver acetate) oxyallyls could be generated from the other monobromoketones [fair to excellent yields (30—90%) of cycloadducts could be obtained using a variety of furans] and with *N*-alkoxycarbonylpyrroles, but not with *N*-methylpyrrole. With the latter, alkylated pyrroles were obtained in good yields (50—70%). The reagent mixture thus parallels the reactivity of nonacarbonyldi-iron and zinc–copper couples, and only sodium iodide in conjunction with copper powder gives cycloadducts with *N*-methylpyrrole. Some representative examples of this method are given in the Table and in the Experimental section. Overall, the method appears to offer a viable alternative to the use of dibromoketones and is particularly attractive when the monobromo-ketones are more easily accessible. Furthermore, since 3-bromo-3-arylpropanones can be employed, this opens up a route to simple 2-arylbicyclo[3.2.1]oct-6-en-3-ones (and derivatives), which have not been easily accessible *via* the other methods of forming oxyallyls.

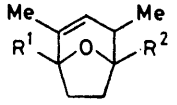
The cycloadducts (4) were hydrogenated using 5% palladium-on-charcoal in methanol–ethyl acetate (1 : 1), and the resultant saturated ketones were reduced with sodium borohydride in ethanol to yield primarily the



(9)



(10)



(11)

a; R^1 = H, R^2 = Me

b; R^1 = H, R^2 = Et

c; R^1 = R^2 = Me

axial alcohols (10). Finally, reaction of these (as a mixture of the axial and equatorial alcohols) with thionyl chloride and pyridine at 0 °C produced olefins of type (11), with approximately equal amounts of the two positional isomers in the case of compounds (11a) and (11b). In the light of our previous finding that the saturated hydrocarbons produced from the olefin mixture (11a) had no biological activity, we submitted the olefins

TABLE

Monobromo-ketone	Diene	Yield [a] (%)
2-Bromopent-3-one	Furan	80
	2-Methylfuran	53
	2-Ethylfuran	65
	2,5-Dimethylfuran	83
	N-Ethoxycarbonylpyrrole	45
	N-Methylpyrrole	67 [b]
2-Bromo- and 4-bromo-hept-3-ones (*ca.* 1 : 1)	Furan	75
	N-Ethoxycarbonylpyrrole	32
1-Bromo-1-phenylbut-2-one	Furan	78 (68) [c]
	N-Ethoxycarbonylpyrrole	39
	N-Methylpyrrole	67 [b]
1-Bromo-1-phenylprop-2-one	Furan	64
	N-Ethoxycarbonylpyrrole	34

[a] Yields quoted are for pure bicyclo[3.2.1]oct-6-en-3-ones with both substituents (where relevant) equatorial. [b] Yield quoted is for pure 2-alkylpyrrole; no cycloadduct formed. [c] Yield when triethylamine was used without silver tetrafluoroborate; mixture of products with (*eq* : *eq* product)/(*eq* : *ax* product) *ca.* 4 : 1.

for biological evaluation. All of them provided good electroantennogram responses (EAG) with male beetles of *Scolytus scolytus*. The responses were similar to those elicited by α-multistriatin itself at dose levels of 10^{-4} g per filter paper disc (dose–response curves parallel), but the threshold for response was higher for our compounds compared with α-multistriatin (10^{-7} compared with 10^{-10} g per filter paper disc). Further biological experiments are in progress.

EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer 157 double-beam grating spectrophotometer (for liquid films unless otherwise stated); ^{1}H n.m.r. spectra were recorded with Varian T-60 (60 MHz) or Varian HA 100 (100 MHz) instruments (tetramethylsilane as internal reference); and mass spectra were recorded on an A.E.I. MS 12 spectro-

meter. Analytical g.l.c. was performed with a Perkin-Elmer F11 gas chromatograph using 8% Carbowax C20M columns. Kieselgel $GF_{254+354}$ (Merck) was used for analytical t.l.c., and Fisons silica gel (80—200 mesh) for column chromatography. Organic solvents were dried over sodium sulphate and removed using a rotary evaporator. The monobromoketones employed were prepared according to literature procedures [7] or, in the case of benzyl alkyl ketones, using *N*-bromosuccinimide in tetrachloromethane with benzoyl peroxide as the initiator.

8-*Oxabicyclo*[3.2.1]*oct*-6-*en*-3-*one* (2).—A solution of 1,1,-3,3-tetrabromopropanone (80 g, 0.21 mol) and triethyl borate (40 ml, 0.25 mol) in tetrahydrofuran (THF) (50 ml) was added slowly to a stirred solution of furan (25 ml, 0.3 mol) in THF (150 ml) containing zinc dust (15 g, 0.21 mol). The mixture was stirred for 2 h at 0 °C under an atmosphere of nitrogen, after which it was allowed to warm to room temperature, and then stirred for a further 16 h. It was then cooled to −60 °C and methanol (60 ml), ammonium chloride (20 g), and zinc dust (15 g) were added, and the whole was allowed to warm to room temperature during 2 h, with vigorous stirring. The solids were filtered off and the filtrate was added to aqueous ammonia (800 ml; 4M), prior to extraction with ether (2 × 250 ml) and dichloromethane (6 × 200 ml). The combined organic extract was dried and concentrated to yield a black oil, which was rapidly filtered through silica gel (100 g) (ether as eluant). The concentrated eluate was taken up in methanol (20 ml) and treated with a zinc–copper couple (50 g) in methanol (100 ml) containing ammonium chloride (10 g) at room temperature. After filtration and addition of dilute hydrochloric acid (500 ml; 2M), the product was extracted into dichloromethane (5 × 100 ml). The final yield of the oil (2) (which rapidly darkened in the freezer, even under an atmosphere of nitrogen) was 27%, R_F 0.2 (ether) and R_T 6 min at 130 °C and 15 lb in^{-2} of nitrogen; $\nu_{max.}$ 3 080w (olefinic CH), 2 960, 2 905, 1 710 (ketone C=O), 1 340, 1 180, 945, 845, and 710 cm (*cis*-olefinic); δ($CDCl_3$) 2.4 (2 H, dd, *J* 17 and 1 Hz, *eq*-CHCO), 2.6 (2 H, dd, *J* 17 and 5 Hz, *ax*-CHCO), 5.1 (2 H, d, *J* 6.5 Hz, bridgehead CH), and 6.3 [2 H, s (on expansion d, *J* 0.5 Hz), CH=CH]; *m/e* (%) 124 (M^+, 80), 95 (10), 82 (90), 81 (100), 68 (10), and 54 (50). The n.m.r. spectrum of this compound is a clear example of an ABX system.

8-*Oxabicyclo*[3.2.1]*octan*-3-*one*.—A solution of the ketone (2) (1.54 g, 10 mmol) in methanol (30 ml) was flushed with nitrogen, 10% palladium-on-charcoal (100 mg) was added, and the flask was evacuated and filled with hydrogen. Hydrogenation was complete after 16 h, after which the catalyst was filtered off and the solution was concentrated. The product, an oil, was obtained in 95% yield; g.l.c R_T 5.5 min at 130 °C, 15 lb in^{-2}; $\nu_{max.}$ 2 960, 2 920, 2 880, 1 717 (ketone C=O), 1 470, 1 405, 1 195, 1 055, and 910 cm^{-1}; δ($CDCl_3$) 1.7 and 2.0 (4 H, m, CH_2CH_2), 2.25 (2 H, dd, *J* 16 and 1 Hz, *eq*-CHCO), 2.65 (2 H, dd, *J* 16 and 5 Hz, *ax*-CHCO), and 4.7 (2 H, m, bridgehead CH); *m/e* (%) 126 (M^+, 70), 98 (15), 97 (20), 83 (50), 69 (60), 58 (70), 55 (100), and 43 (90).

8-*Oxabicyclo*[3.2.1]*octan*-3-*one Oxime* (5).—The ketone (2) (1.15 g, 9 mmol) was dissolved in a solution of hydroxylamine hydrochloride (1 g) and sodium acetate (1 g) in water (20 ml) by the addition of ethanol (*ca.* 10 ml). The mixture was refluxed for 2 h and then cooled and extracted with dichloromethane. With time, the oxime (5) crystallised from the concentrated organic extracts. Recrystallization from chloroform and hexane gave white needles of the *oxime* (5), m.p. 74 °C, yield 80%; R_F 0.6 (ether); $\nu_{max.}$ 3 300 (oxime OH), 2 950, 2 910, 1 655 (oxime C=N), 1 300, 1 160, 865, and 730 cm^{-1}; δ($CDCl_3$) 1.8 (4 H, m, CH_2CH_2), 2.2 (1 H, d, *J* 15 Hz, H_a), 2.25 (1 H, dd, *J* 15 and 4 Hz, H_b), 2.6 (1 H, dd, *J* 15 and 4 Hz, H_c), 3.05 (1 H, d, *J* 15 Hz, H_d), 4.55 (2 H, bridgehead CH), and 9.6 (1 H, br s, disappears with D_2O, C=NOH); *m/e* (%) 141.0789 (M^+, 15), 124 (50), 96 (25), 81 (25), 73 (100), and 57 (100); $C_7H_{11}NO_2$ requires *M*, 141.0790.

9-*Oxa*-3-*azabicyclo*[4.2.1]*nonan*-4-*one* (6).—The lactam (6) was prepared by heating the oxime (5) (1.0 g, 7 mmol) at 80 °C for 2 h in a mixture of methanesulphonic acid (4.5 g) and phosphorus pentaoxide (0.5 g). The reaction was quenched by carefully pouring the cooled mixture into a cold solution of sodium hydrogencarbonate. Chloroform extraction of the hydrogencarbonate solution gave a brown oil in 80% yield. The oil solidified on addition of dichloromethane and the *lactam* (6) was subsequently recrystallized from this solvent as white needles, m.p. 164 °C, yield 60%; R_F 0.3 (10% of methanol in ether); $\nu_{max.}$ 3 250 (lactam N–H), 2 960, 2 920, 1 660 (lactam C=O), 1 420, 1 070, and 800 cm^{-1}; δ($CDCl_3$) 2.0 (4 H, m, CH_2CH_2). 2.6 (1 H, ddd, *J* 16, 4.5, and 2 Hz, H_a), 2.85 (1 H, dd, *J* 16 and 2 Hz, H_b), 2.95 (1 H, dd, *J* 15, 8, and 4 Hz, H_c), 3.7 (1 H, dd, *J* 15 and 2 Hz, H_d), 4.4 (2 H, m, H_e and H_f), and 6.4 (1 H, br m, NH); *m/e* (%) 141.0791 (M^+, 3), 140 (15), 133 (15), 111 (60), 96 (40), 79 (60), and 55 (100); $C_7H_{11}NO_2$ requires *M* 141.0790.

cis-2-(*Aminomethyl*)-5-(*carboxymethyl*)*tetrahydrofuran* (7a).—The lactam (6) (0.56 g, 4 mmol) was hydrolysed by refluxing in 12% hydrochloric acid (20 ml) for 2 h. The hydrochloric acid was removed by distillation on a water-pump and the amino-acid hydrochloride, a glassy solid, was re-dissolved in water (10 ml) and passed through an ion exchange resin, IR 45 (OH). The resin was washed with a further portion of distilled water (80 ml). Concentration of the eluate gave the amino-acid (7a), in 80% yield as white cubic crystals, m.p. 184 °C; $\nu_{max.}$ 3 450 (ammonium NH), 2 950, 2 920, 1 570 and 1 400 (carboxylate CO_2^-), 1 200, and 1 050 cm^{-1}; δ(D_2O) 1.9 (4 H, m, CH_2CH_2), 2.4 (2 H, d, *J* 7 Hz, CH_2CO_2), 3.0 (2 H, m, CH_2N), 4.2 (2 H, m, CHOCH), and 4.5 (s, HOD); *m/e* (%) M^+ absent, 142 (5), 129 (28), 111 (51), 83 (38), and 55 (100).

cis-2-(*Methoxycarbonylmethyl*)-5-(*trimethylammoniomethyl*)*tetrahydrofuran Iodide* (8a).—The amino-acid (7a) (0.5 g, 3 mmol) was treated with methyl iodide (1 ml) in methanol (1 m) containing potassium carbonate (1 g) at room temperature for 16 h. Soxhlet extraction of the concentrated reaction mixture with chloroform gave the desired muscarine analogue [529] (8a) as a 'low melting' brownish solid, yield 50%; $\nu_{max.}$ 1 730 (ester C=O), 1 645, 1 090, 1 020, 920 (trimethylammonium), and 810 cm^{-1}; δ($CDCl_3$) 1.75 and 2.25 (4 H, m, CH_2CH_2), 2.6 (2 H, d, *J* 7 Hz, CH_2CO_2), 3.5 (9 H, s, NMe_3), 3.7 (3 H, s, CO_2Me), 4.2 (2 H, dd, *J* 12 and 1 Hz, CH_2N), 4.4 (1 H, t, *J* 7 Hz, CHO), and 4.45 (1 H, br m, $OCHCH_2N$); *m/e* (%) M^+ absent, 201.2636 (M^+ − MeI, 1), 142 (18), 141 (10), 127 (10), 113 (10), 111 (13), 105 (43), 97 (10), 83 (30), 58 (100), and 53 (60); $C_{10}H_{19}NO_3$ requires (M − MeI) 201.266.

cis-2-(1-*Aminoethyl*)-5-(1-*carboxyethyl*)*tetrahydrofuran* (7b).—Prepared in 90% yield from the corresponding lactam as white needles, m.p. 216 °C; $\nu_{max.}$ 3 400br (acid OH and amine NH), 2 500 and 2 100w, 1 710w, (acid C=O), 1 630 (amine CN), 1 550 (carboxylate and NH_3^+), 1 450,

and 1 060 cm^{-1}; δ(D_2O) 1.1 (3 H, d, *J* 7 Hz, $^{-}O_2CCHMe$), 1.27 (3 H, d, *J* 7 Hz, D_3N^+CHMe), 2.0 and 2.4 (4 H, m, CH_2CH_2), 2.72 (1 H, dq, *J* 7 and 7 Hz, $CHCO_2$), 3.5 (1 H, dq, *J* 4 and 7 Hz, $CHND_3^+$), and 4.1 (2 H, m, CHOCH); *m/e* (%) 187.1204 (M^+, 3), 169 (30), 141 (60), 98 (70), 70 (70), 69 (80), and 55 (100); $C_9H_{17}NO_3$ requires *M* 187.1208.

cis-2-(1-*Methoxycarbonylethyl*)-5-(1-*trimethylammonioethyl*)*tetrahydrofuran Iodide* (8b).—The amino-acid (7b) (1 g, 5.2 mmol) was stirred with potassium carbonate (1 g) and methyl iodide (2.5 ml) in methanol (5 ml) for 16 h. The solvents were removed and the product was extracted into chloroform using a Soxhlet apparatus. The extract was dried and concentrated to yield a yellowish oil which crystallised with time to give the *iodide* (8b), m.p. 137 °C (Found: C, 43.66, H 7.87%, N, 4.11%. $C_{13}H_{26}INO_3$ requires C 43.66%, H 8.09%, N 4.07%); $\nu_{max.}$ (Nujol mull) 1 730 (ester C=O), 1 260, 1 050, and 960 cm^{-1} (trimethylammonium); δ($CDCl_3$) 1.18 (3 H, d, *J* 7 Hz, Me), 1.37 (3 H, dt, *J* 6.5 and 2 Hz, NCH*Me*), 1.7—2.2 (4 H, m, CH_2CH_2), 2.6 (1 H, dq, *J* 7 and 7 Hz, $CHCO_2$), 3.46 (9 H, s, NMe_3), 3.66 (3 H, s, CO_2Me), 4.05 (1 H, ddd, *J* 6, 6, and 6 Hz, $CHCHCO_2$), 4.32 (1 H, q, *J* 6.5 Hz, CHN), and 4.62 (1 H, m, *CH*CHN); *m/e* (%) M^+ absent, 229.1673 (M^+ — MeI, 1), 212 (5), 198 (5), 142 (30), 127 (35), 98 (25), 72 (100), and 70 (20); $C_{12}H_{23}NO_3$ requires (M — MeI) 229.1678.

General Procedure for Cycloadditions using Silver Tetrafluoroborate.—A solution of the mono-α-bromo-ketone (10 mmol) in acetonitrile (5 ml) was added to a stirred solution of silver tetrafluoroborate (1.94 g, 10 mmol) in acetonitrile (20 ml) and stirring was continued for 6—8 h under an atmosphere of nitrogen and in the dark. The flask was then cooled to −10 °C and a mixture of the cyclic diene (usually a furan) (12 mmol) and triethylamine (1 ml) in acetonitrile (5 ml) was added during 30 min. The mixture was then stirred at room temperature for 16 h, before work-up using water (20 ml) and dichloromethane (25 ml). The organic layer was separated and the aqueous layer extracted once with dichloromethane (15 ml). The combined organic extract was dried and concentrated to give an oil prior to chromatography over silica. The following products were obtained (see ref. 4).

(a) 1,2,4-*Trimethyl*-8-*oxabicyclo*[3.2.1]*oct*-6-*en*-3-*one* (4a). The compound (4a) was obtained in 53% yield as an oil; $\nu_{max.}$ 3 080, 2 980, 2 940, 2 880, 1 710, 1 598, 1 375, 1 165, 890, and 740 cm^{-1}; δ($CDCl_3$) 0.95 (3 H, d, *J* 7 Hz, Me), 1.00 (3 H, d, *J* 7 Hz, Me), 1.50 (3 H, s, Me), 2.60 (1 H, q, *J* 7 Hz, MeC*H*), 2.65 (1 H, dq, *J* 5 and 7 Hz, MeC*H*), 4.85 (1 H, dd, *J* 5 and 1.5 Hz, C*H*—O), 6.10 (1 H, d, *J* 6 Hz, CH=), and 6.25 (1 H, dd, *J* 6 and 1.5 Hz, CH=); *m/e* 166 (M^+), 151, 109, 95, 81, 53, and 43.

(b) 1-*Ethyl*-2,4-*dimethyl*-8-*oxabicyclo*[3.2.1]*oct*-6-*en*-3-*one* (4b). Compound (4b) was obtained in 65% yield as an oil; $\nu_{max.}$ 3 080, 2 960, 1 710, 1 460, and 740 cm^{-1}; δ($CDCl_3$) 0.97 (3 H, t, *J* 7 Hz, *Me*CH_2), 0.90 and 0.93 (6 H, 2 d, *J* 7 Hz, 2 × Me), 1.88 (2 H, q, *J* 7 Hz, MeCH_2), 2.60 (1 H, q, *J* 7 Hz, MeC*H*), 2.77 (1 H, dq, *J* 7 and 5 Hz, MeC*H*), 4.86 (1 H, dd, *J* 5 and 2 Hz, CH—O), 6.07 (1 H, d, *J* 6 Hz, CH=), and 6.18 (1 H, dd, *J* 6 and 2 Hz, CH=); *m/e* 180 (M^+), 165, 151, 124, 123, 109, and 95.

(c) 1,2,4,5-*Tetramethyl*-8-*oxabicyclo*[3.2.1]*oct*-6-*en*-3-*one* (4c). Compound (4c) was obtained as a pale white crystalline solid, m.p. 69—70 °C, in a yield of 83%; $\nu_{max.}$ (Nujol mull) 3 060, 2 980, 2 880, 1 705, 1 450, 1 375, 1 340, 1 160, and 750 cm^{-1}; δ($CDCl_3$) 1.00 (6 H, d, *J* 7 Hz, Me), 1.48 (6 H, s, Me), 2.6 (2 H, q, *J* 7 Hz, MeC*H*—), and 6.02 (2 H, s, CH=); *m/e* 180.249 (M^+; Calc. for $C_{11}H_{16}O_2$ 180.249), 165, 123, and 109.

1,2,4-*Trimethyl*-8-*oxabicyclo*[3.2.1]*oct*-2-*ene and* -3-*ene* (11a).—The cycloadduct (4a) was hydrogenated over 5% palladium-on-charcoal to produce the corresponding alkane in 98% yield. This was reduced with sodium borohydride in ethanol to produce a mixture of the alcohols (10a) in 85% yield. The ratio at the axial and equatorial alcohols was shown to be 85 : 15 by n.m.r. [δ 3.4 (1 H, t, *J* 8 Hz, C*H*OH of equatorial alcohol) and 3.7 (1 H, t, *J* 4 Hz, C*H*OH of axial alcohol)]. The crude mixture was dissolved in pyridine, cooled to 0 °C, and treated with an excess of thionyl chloride. After the addition, the mixture was stirred for 3 h at 0 °C, then poured onto ice, and the products were extracted into ether. The organic layer was washed successively with copper sulphate solution and water (× 2), and then dried and concentrated to yield a brown oil which was purified by silica chromatography (light petroleum–ether 4 : 1), followed by short-path distillation. The overall yield for this step was 40%. The ratio of the olefin isomers was shown to be *ca.* 1 : 1 by g.l.c.; R_T 13 and 14 min on Carbowax 20M (7%) at 50 °C and 15 lb in^{-2} of nitrogen; $\nu_{max.}$ 3 060, 2 960, 2 930, 2 870, 2 860, 1 450, 1 375, 1 100, 1 030, 885, and 830 cm^{-1}; δ($CDCl_3$) 0.90 and 0.93 (3 H, 2 d, *J* 7 Hz, *Me*CH of two isomers), 1.35 (3 H, s, bridgehead Me), 1.6 (3 H, 2 d, *J* 2 Hz, MeC= of two isomers), 1.9 (4 H, br m, CH_2CH_2), 2.5 (1 H, m, MeC*H*), 4.2 (1 H, m, CH—O), and 5.0 (1 H, m, CH=); *m/e* 152 (M^+), 137, 123, 109, 95, 81, 79, and 67.

1-*Ethyl*-2,4-*dimethyl*-8-*oxabicyclo*[3.2.1]*oct*-2-*ene and* -3-*ene* (11b).—Compounds (11b) and the oct-2-ene isomer were prepared by the same procedure as outlined above, as *oils*; $\nu_{max.}$ 3 050, 2 925, 1 460, and 1 380 cm^{-1}; δ($CDCl_3$) (100 MHz) 0.78 and 0.85 (total 3 H, 2 d, for two isomers, *ca.* 1 : 1, *Me*CH), 0.94 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.59 and 1.62 (total, 2 d, 3 H, *J* 2 Hz, MeC=), 1.60—2.00 (6 H, m, CH_2CH_2 and MeCH_2), 2.75 (1 H, m, MeC*H*), 4.20 (1 H, m, CH—O), and 4.98 and 5.04 (total 1 H, 2 dd, *J* 2 and 2 Hz, CH=); *m/e* 166.1342 (M^+; $C_{11}H_{18}O$ requires 166.264), 137.0979 (M^+ — Et), and 57.0367 (100%, Pr^nO^+).

1,2,4,5-*Tetramethyl*-8-*oxabicyclo*[3.2.1]*oct*-2-*ene* (11c).—Compound (11c) was prepared as outlined for compound (11a), as an *oil*; $\nu_{max.}$ 3 060, 2 935, 1 450, and 1 377 cm^{-1}; δ(CD-Cl_3) (100 MHz) 0.90 (3 H, d, *J* 7 Hz, Me), 1.35 and 1.38 (6 H, 2 × s, MeC—O), 1.60 (3 H, dd, *J* 2 and 2 Hz, MeC=), 5.00 (1 H, m, CH=); *m/e* 166.1345 (M^+; $C_{11}H_{18}O$ requires 166.264), 123.1116 (M^+ — EtO, 100%), and 81.0702 ($C_6H_9^+$).

We thank the S.R.C. and Glaxo-Allenbury for a CASE award (A.P.C.) and Food, Drug and Cosmetic Colours Ltd for a studentship (A.A.U.).

[1/056 *Received*, 14*th January*, 1981]

REFERENCES

1 A. P. Cowling and J. Mann. *J. Chem. Soc., Perkin Trans. 1*, 1978, 1564.
2 M. M. Blight, F. A. Mellon, L. J. Wadhams, and M. J. Wenham, *Experientia*, 1977, **33**, 845.
3 H. M. R. Hoffmann and M. N. Iqbal, *Tetrahedron Lett.*, 1975, 2048.
4 Y. Hayakawa, R. Kobayashi, S. Murai, R. Noyori, N. Sonoda, and H. Takaya, *J. Am. Chem. Soc.*, 1978, **100**, 1759.
5 R. D. Allan and B. Twitchin, *Aust. J. Chem.*, 1980, **33**, 599.
6 John Mann and A. A. Usmani, *J. Chem. Soc., Chem. Commun.*, 1980, 1119.
7 D. P. Bauer and R. S. Macomber, *J. Org. Chem.*, 1975, **40**, 1990.
8 B. Fohlisch, W. Gottstein, R. Kaiser, and I. Wanner, *Tetrahedron Lett.*, 1980, **21**, 3005.