The Oxyallyl Cation in Synthesis: Preparation of Analogues of Cocaine

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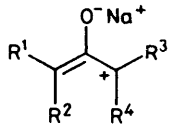
An attempt has been made to establish the synthetic utility of cycloaddition reactions involving the oxyallyl cation R^1R^2C=CO^-M^+ R^3R^4C (1a). Reactions of this intermediate (R^1,R^3 = alkyl; R^2,R^4 = H; and M = Na) with furan and *N*-methylpyrrole were particularly facile, and have been used for the synthesis of a number of novel analogues of cocaine. Although some of the cycloaddition products have been reported by other workers, there has always been a paucity of experimental details. We provide herein full experimental details for our reactions, and also a tabular survey of methods used and results obtained.

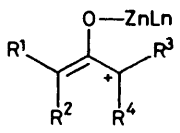
SINCE the pioneering work of Cookson,[1] Hoffmann,[2] and Noyori[3] on the preparation and reactions of oxyallyl cations of general formula (1), these intermediates have been little used in synthesis. They react with many dienes to produce seven-membered rings, and their synthetic potential seems to be limited only by the availability or reactivity of the parent α,α'-dibromoketones (2). At the commencement of our work, Noyori had used these 3 + 4 ($_2\pi + _4\pi$) cycloadditions to prepare carbocamphenilone from 1,1,3-tribromo-3-methylbutanone and cyclopentadiene;[4] while Hoffmann had carried out syntheses of karahanaenone from 1,3-dibromo-3-methylbutanone and isoprene,[5] and of the dehydrotropinone (3) from 2,4-dibromopentanone and *N*-methylpyrrole;[6] but this was the limit of the (published) synthetic applications. [Since this time, White[7] has used the cycloadduct formed from 2,4-dibromopentanone and furan for a synthesis of (±)-nonactic acid, and Meinwald[8] has synthesised pederin using the cycloadduct formed from 1,3-dibromo-3-methylbutanone and furan].

Initially we wished to compare the reactivities of oxyallyl cations with *N*-methylpyrrole, furan, and thiophen as diene components, in order to assess the likely utility of these cycloadditions for the construction of

[1] R. C. Cookson, M. J. Nye, and G. Subrahmanyam, *J. Chem. Soc.* (*C*), 1967, 473.
[2] H. M. R. Hoffmann, D. R. Joy, and A. K. Suter, *J. Chem. Soc.* (*B*), 1968, 57.
[3] R. Noyori, S. Makino, and H. Takaya, *J. Amer. Chem. Soc.*, 1971, **93**, 1272.
[4] R. Noyori, T. Souchi, and Y. Hayakawa, *J. Org. Chem.*, 1975, **40**, 2681.
[5] H. M. R. Hoffmann, *Angew. Chem. Internat. Edn.*, 1973, 12, 819.
[6] H. M. R. Hoffmann, R. Chidgey, and G. Fierz, *Angew. Chem. Internat. Edn.*, 1974, **13**, 410.
[7] M. J. Arco, M. H. Trammell, and J. D. White, *J. Org. Chem.*, 1976, **41**, 2075.
[8] J. Meinwald, *Pure and Appl. Chem.*, 1977, **49**, 1275.

novel heterocyclic systems. An obvious approach was to extend Hoffmann's work on tropinones to produce oxa- and thia-analogues and thence analogues of cocaine (4)


(1a)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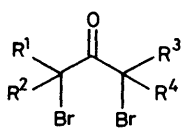
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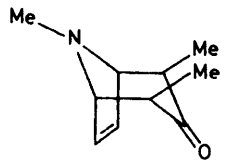
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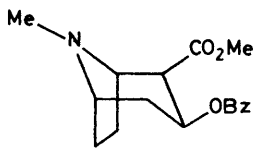
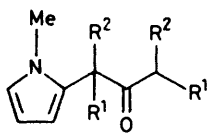
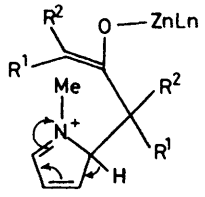

(4)


(5a) R^1 = H, R^2 = Me
(5b) R^1 = H, R^2 = Ph


(6)

by further synthetic transformation. These it was hoped would have interesting biological activities.

A number of different methods of generating the oxyallyl cations were tried, including nona-carbonyldi-iron,[3] zinc–copper couple,[2] zinc with triethyl borate,[9] and copper powder with sodium iodide.[6] With *N*-methylpyrrole as diene this latter method was very effective when 2,4-dibromopentanone was used (as reported by Hoffmann [6]), and the expected cycloadduct (3) was obtained in fair yield (50—60%): no pyrrolic products were obtained. Zinc-based reagents yielded very little of the cycloadduct, but gave mainly the pyrrole (5a). Use of nonacarbonyldi-iron resulted in the production of intractable mixtures. Other similar dialkyl-α,α′-dibromo-ketones behaved in the same way, when treated with *N*-methylpyrrole in the presence of these reagents.

When we turned our attention to other kinds of dibromo-ketones, *viz.* 2,4-dibromo-2,4-dimethylpentanone, 1,3-dibromo-1,3-diphenylpropanone, and 2,6-dibromocyclohexanone, we found that pyrrolic products were formed exclusively under all conditions tried. Cookson [1] had previously reported that 1,3-dibromo-1,3-diphenyl-propanone when heated for long periods in the presence of sodium iodide and *N*-methylpyrrole gave the product (5b). In addition we found that the cycloadduct (3) was not affected by treatment with zinc–copper couple, or by zinc and sodium iodide, and we infer that the zinc-based reagents are not responsible for ring-opening of an initially formed cycloadduct, to yield the observed product (5a).

[9] H. M. R. Hoffmann and M. N. Iqbal, *Tetrahedron Letters*, 1975, 4487.

We can offer no totally convincing explanation for these results, but believe that they can be explained in terms of the differing stabilities or reactivities of the oxyallyl cations (1a) and (1b); and that two separate mechanisms may be operating, dependent upon the metal used. Certainly the zinc enolate will have greater covalent character than the ionic sodium enolate (1a). Hoffmann has recently suggested [10] that when zinc–copper couple is employed a two-step reaction occurs, and with *N*-methylpyrrole an intermediate like (6) could be involved. Subsequent ring closure is likely to be unfavourable, and pyrroles (5) should result. With copper and sodium iodide rapid exchange of bromo for iodo probably occurs, and subsequent dehalogenation assisted by copper leads to the oxyallyl cation (1a). In addition, when the intermediate is formed from simple dialkyl-dibromo-ketones (R^1,R^3 = alkyl, R^2,R^4 = H) there should be less tendency for localisation of the positive charge on either α-carbon atom (compare with the species formed from 1,3-dibromo-1,3-diphenyl-propanone and from 2,4-dibromo-2-methylpentanone), and concerted cycloaddition of (1a) may be favoured, even when a relatively unreactive diene like *N*-methyl-pyrrole is co-reactant.

With the more reactive diene furan, however, cyclo-adducts were formed in good yields from all of the aforementioned dibromo-ketones, using either copper powder with sodium iodide or zinc–copper couple. This system thus provides a useful route to bicyclo[3.2.1]-octenones, and compounds that can be derived from them.

Initial experiments with thiophen were not promising: complex mixtures of products were produced with several dibromo-ketones, and this system has not as yet been studied further.

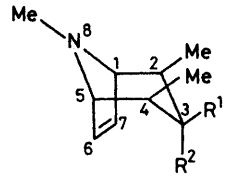
The 6,7-dehydrotropinone (3) was reduced with lithium aluminium hydride to yield an approximately 2 : 1 mixture of the alcohols (7) and (8), and benzoylation of this mixture of alcohols was accomplished by heating with benzoic anhydride in refluxing toluene for two days. The resultant benzoates (9) and (10) ($J_{2,3}$ 5.5 Hz and 10 Hz respectively, consistent with $H_{ax.}$–$H_{eq.}$ and $H_{ax.}$–$H_{ax.}$ couplings) were hydrogenated to produce the cocaine analogues (11) and (12). This sequence of reactions was repeated, commencing with the cyclo-adduct from 2,4-dibromoheptan-3-one and *N*-methyl-pyrrole to obtain the analogues (13) and (14); and with the cycloadduct from 2,4-dibromopentanone and furan to produce compounds (15) and (16).

Most of these compounds were tested for analgetic activity, and compounds (10) and (12) were approxi-mately equipotent with codeine in several tests but were, however, more toxic than cocaine, and thus of no practical use. All the other compounds tested were essentially inactive as analgesics.

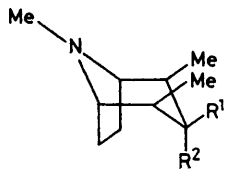
Two additional experiments were carried out in this series: reaction of *N*-benzylpyrrole with the oxyallyl

[10] H. M. R. Hoffmann and R. Chidgey, *Tetrahedron Letters*, 1978, 85.

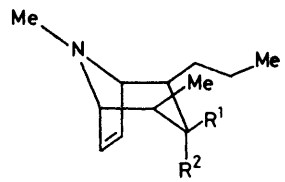
cation from 2,4-dibromopentanone, and an attempted epoxidation of (9) to produce an analogue of scopolamine. The cycloaddition proceeded in good yield to



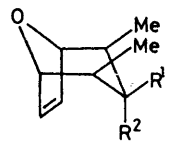
(7) R^1 = H, R^2 = OH
(8) R^1 = OH, R^2 = H
(9) R^1 = H, R^2 = OBz
(10) R^1 = OBz, R^2 = H



(11) R^1 = H, R^2 = OBz
(12) R^1 = OBz, R^2 = H



(13) R^1 = H, R^2 = OBz
(14) R^1 = OBz, R^2 = H



(15) R^1 = H, R^2 = OBz
(16) R^1 = OBz, R^2 = H

produce the expected adduct with both methyls equatorial, together with some axial-equatorial isomers (*ca.* 25% of the total). These isomers were also observed in reactions with furans (up to 34% of total products), but never with *N*-methylpyrrole.

Attempted epoxidation of (9) with *m*-chloroperbenzoic acid gave the *N*-oxide (N–Me signal in the n.m.r. shifted downfield to 3.70 p.p.m.), but no epoxide. The use of peracetic acid or pertrifluoroacetic acid led to decomposition of the starting cycloadduct; and reagents producing Br^+ did not react with (9).

In summary, our experiences with oxyallyl cations have indicated that simple α,α′-dibromo-ketones like 2,4-dibromopentanone are the best precursors of these species, and that furan is a particularly good acceptor molecule. These results are summarised in the Table.

* *Note added in proof*: Noyori has now provided experimental details of all of his early work using nonacarbonyldi-iron (R. Nayori, *J. Amer. Chem. Soc.*, 1978, **100**, 1759). The only result which has particular relevance to the present work is that *N*-methylpyrrole failed to give cycloadducts under his reaction conditions. Various alkylpyrroles were obtained instead, a result in agreement with our findings when using zinc–copper couple to generate the oxyallyl intermediate. Hence for *N*-alkyl-, or *N*-aryl-pyrroles, copper and sodium iodide should be used, while for furans, this reagent or zinc–copper couple are the cheapest and easiest. Nonacarbonyldi-iron must be freshly prepared from the very toxic pentacarbonyliron (by u.v. irradiation using large volumes of glacial acetic acid as solvent), and usually offers no advantage over these simpler reagents.

All our more recent synthetic endeavours have been carried out with furans, and this work will be reported separately.*

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 with a Varian T-60 (60 MHz) instrument or with a Varian HA100 (100 MHz) spectrometer (tetramethylsilane as internal reference); and mass spectra with an A.E.I. MS12 spectrometer. Analytical g.l.c. was performed with a Perkin-Elmer F11 gas chromatograph. Kieselgel $GF_{254+354}$ (Merck) was used for analytical t.l.c. (0.25-mm layers) and for preparative t.l.c. (1-mm layers). Fison's silica gel (80—200 mesh) was employed for column chromatography. Organic solvents were dried over anhydrous magnesium sulphate and removed with a rotary evaporator.

General Procedure for Cycloadditions.—A solution of diene (12 mmole) and dibromo-ketone (10 mmol) in acetonitrile (20 ml) was added during a 30-min period to a solution of sodium iodide (6 g, 40 mmol) in acetonitrile (50 ml) containing copper powder (copper reduced by hydrogen as supplied ex. B.D.H.) (1.9 g, 30 mmol). The mixture was stirred magnetically and maintained under an atmosphere of nitrogen throughout the experiment. After 8 h, water (25 ml) and dichloromethane (50 ml) were added, and the mixture was stirred vigorously for 10 min to precipitate cupric iodide, and was then filtered. The filtrate was washed successively with dilute ammonia solution and then with brine after which the organic layer was separated, dried ($MgSO_4$), and concentrated.

The dibromo-ketones were prepared as follows. Bromine (52 ml, 1 mol) was added to a solution of ketone (1 mol) in hydrobromic acid (50 ml, 48%) and the mixture was stirred overnight. After successive washings with sodium bisulphite solution, sodium hydrogen carbonate solution, and with brine, the crude product was fractionally distilled using a 10-cm Vigreux column. B.p.s and spectral data were in agreement with those reported by Hoffmann.[11]

2,4,8-*Trimethyl*-8-*azabicyclo*[3.2.1]*oct*-6-*en*-3-*one* (3).—This dehydrotropinone was prepared by the above procedure from 2,4-dibromopentanone and *N*-methylpyrrole; after partial purification by extraction of the product into cold 2N-hydrochloric acid, and back extraction into dichloromethane after neutralisation, it was further purified by fast filtration through silica gel using ether as eluant. Yields of between 50 and 60% were obtained on reaction scales varying from 0.01 to 0.1 mol. The product (5) was rather unstable and was usually used without further purification. A sample of at least 95% purity was obtained by preparative t.l.c. and had the following spectral characteristics: $\nu_{max.}$ 3 055, 1 705, and 707 cm^{-1}; δ($CDCl_3$) 1.0 (6 H, d, *J* Hz, Me), 2.3 (3 H, s, NMe), 2.7 (2 H, m, COCH), 3.5 (2 H, d, *J* 4 Hz, bridgehead CH), and 6.1 (2 H, d, *J* 0.5 Hz, CH=CH); *m/e* 165 (M^+, 25), 108 (100), and 94 (50).

2,4,8-*Trimethyl*-8-*azabicyclo*[3.2.1]*oct*-6-*en*-3-*ols* (7) *and* (8).—A solution of the ketone (3) (1.69 g, 10 mmol) in dry ether (15 ml) was refluxed with lithium aluminium hydride (0.11 g, 2.7 mmol) for 6 h. The product was obtained following slow addition of sodium hydroxide solution (3M) at

[11] H. M. R. Hoffmann and J. G. Vinter, *J. Org. Chem.*, 1974, **39**, 3921.

0 °C, and extraction of the resultant granular precipitate with several aliquots of ether. This provided a mixture of the alcohols (7) and (8) as an oil in a ratio of *ca.* 2 : 1 (7 : 8) as judged by n.m.r. (singlets for CH=CH at 6.30 and 6.00 p.p.m. respectively). The overall yield was at least 90%. This mixture was used without further purification.

2,4,8-Trimethyl-8-azabicyclo[3.2.1]*oct-6-en-3-yl Benzoates* (9) *and* (10).—The alcohol mixture (1.7 g, 10 mmol) was refluxed in dry toluene (50 ml) with benzoic anhydride (3.0 g, 13 mmol) for 36 h. Isolation was effected by addition of ether (25 ml), extraction into cold 2M-hydrochloric acid, neutralisation, and extraction into dichloromethane. The crude products were purified by column chromatography with gradient elution from 10% to 40% methanol in ether. This provided a 20% yield of pure benzoates (9) and (10) with a *ca.* 40% recovery of the alcohols. Upon recycling, the yield of benzoates could be raised to 33%, and the ratio of (9) to (10) was *ca.* 3 : 5. Spectral data for the axial benzoate (9) are: $\nu_{max.}$ 3 060, 2 960, 2 930, 2 880, 2 785, 1 715, 1 600, 1 585, and 710 cm^{-1}; $\delta(CDCl_3)$ 0.85 (6 H, d, *J* 7 Hz, Me), 2.4 (2 H, m, C*H*Me), 2.3 (3 H, s, NMe), 3.2 (2 H, m, bridgehead CH), 5.4 (1 H, t, *J* 5.5 Hz, CHO), 6.25 (2 H, s, CH=CH), and 7.4—8.0 (5 H, m, Ph); *m/e* 271.157 5 (M^+, 10), 164 (15), 108 (100), 105 (40), and 94 (80) ($C_{17}H_{21}NO_2$ requires 271.157 2). The benzoate was a white crystalline solid, m.p. 57 °C.

Spectral data for the equatorial benzoate (10) are: $\nu_{max.}$ 3 060, 2 960, 2 925, 2 885, 2 780, 1 715, 1 600, 1 590, and 710 cm^{-1}; $\delta(CDCl_3)$ 0.87 (6 H, d, *J* 7 Hz), 2.1 (2 H, m, C*H*Me), 2.3 (3 H, s, NMe), 3.4 (2 H, m, bridgehead CH), 4.8 (1 H, t, *J* 10 Hz, CHO), 6.05 (2 H, s, CH=CH), and 7.4—8.10 (5 H, m, Ph); *m/e* 271.158 3 (M^+, 6), 149 (15), 108 (50), 105 (20), and 84 (100) ($C_{17}H_{21}NO_2$ requires 271.157 2). The benzoate was a colourless oil.

In biological tests compounds (10) had analgetic activity comparable to that of codeine in three tests, and also had greater antipyretic activity than paracetamol. Compound (9) was essentially inactive.

2,4,8-Trimethyl-8-azabicyclo[3.2.1]*octan-3-yl Benzoates* (11) *and* (12).—The benzoates (11) and (12) were obtained from (9) and (10) respectively by catalytic hydrogenation over 10% palladium on charcoal using dry methanol as solvent. Filtration and evaporation of solvent gave pure samples of the saturated benzoates in yields of *ca.* 75%; m.p.s 64 °C (11) and 187 °C (12). Spectral data for the axial benzoate (11) are: $\nu_{max.}$ 2 960, 2 930, 2 876, 1 715, 1 600, 1 585, 1 270, and 710; $\delta(CDCl_3)$ 0.90 (6 H, d, *J* 7 Hz, Me), 1.7—2.6 (6 H, m, CH and CH_2), 2.3 (3 H, s, NMe), 2.8 (2 H, m, bridgehead CH), 5.4 (1 H, t, *J* 4.5 Hz, CHO), and 7.4—8.1 (m, 5 H, Ph); *m/e* 273.171 7 (273, M^+) (5%); 152 (90), 105 (50), 96 (30), 83 (100), and 77 (90) ($C_{17}H_{23}NO_2$ requires 273.172 8).

Spectral data for the equatorial benzoate (12) are: $\nu_{max.}$ 2 960, 2 920, 2 840, 1 719, 1 602, 1 585, and 715 cm^{-1}; $\delta(CDCl_3)$ 0.95 (6 H, d, *J* 7 Hz, Me), 2.1 (3 H, s, NMe), 2.85 (4 H, m, CH_2CH_2), 3.1 (2 H, m, C*H*CH_3), 3.65 (2 H, m, bridgehead CH), 4.85 (1 H, t, *J* 10 Hz, CHO), and 7.4—8.1 (5 H, m, Ph); *m/e* 273.171 2 (M^+, 7%), 152 (80), 105 (50), and 82 (100) ($C_{17}H_{23}NO_2$ requires 273.172 8).

2,8-Dimethyl-4-propyl-8-azabicyclo[3.2.1]*oct-6-en-3-yl Benzoate* (14).—This compound was prepared in an overall yield (including preparative t.l.c.) of 5% from 2,4-dibromoheptan-3-one and *N*-methylpyrrole, using methods identical to those described for the preparation of (10). Spectral data for this oil are: $\nu_{max.}$ 3 060, 2 960, 2 920, 2 870, 2 780, 1 715, 1 600, 1 585, and 705; $\delta(CDCl_3)$ 0.93 (3 H, t, 7 Hz, propyl Me), 0.95 (3 H, d, *J* 7 Hz, Me), 1.3 (4 H, m, CH_2CH_2), 2.0 (2 H, m, CH), 2.3 (3 H, s, NMe), 3.4 and 3.6 (2 H, m's, bridgehead CH), 4.7 (1 H, t, 8 Hz, C*H*O), 6.1 (2 H, s, CH=CH), and 7.5—8.1 (5 H, m, Ph); *m/e* 299 (M^+, 40%), 178 (30), 136 (100), 108 (100), 105 (100), and 94 (100).

The compound was essentially inactive in the primary analgetic screen.

2,4-Dimethyl-8-oxabicyclo[3.2.1]*oct-6-en-3-yl Benzoate* (15).—This 8-oxa-analogue was prepared according to the general method for the synthesis of (3) except that furan was used in place of *N*-methylpyrrole, and purification of the cycloadduct was achieved by chromatography on silica gel using light petroleum (b.p. 40—60 °C) and diethyl ether (4 : 1 ratio by volume) as eluant. The yields obtained were somewhat better (60—75%) than those obtained with *N*-methylpyrrole. The cycloadduct (8-oxa-analogue of (3)) was reduced with lithium aluminium hydride in ether to produce an 80% yield of the alcohols. These were treated with benzoic anhydride and triethylamine (1.5-fold excess) in refluxing toluene for 180 h, and chromatography of the product mixture on silica gel with light petroleum–diethyl ether (4 : 1), furnished a pure sample of

Percentage yields of isolated products

		N-Methylpyrrole		Furan	
Bromo-ketone	Reagent	Cycloaddition	Alkylation	Cycloaddition	Alkylation
2,4-Dibromopentanone	Cu–NaI	52	None	75	None
	Zn–Cu	None	60	70	None
2,4-Dibromoheptan-3-one	Cu–NaI	57	None		
	Zn–Cu	None	60		
1,1,3,3-Tetrabromopropanone	Cu–NaI	None	None	None	None
	Zn–Cu	None	None	None	None
	Zn–$(EtO)_3B$			30	None
1,3-Dibromopentan-2-one	Cu–NaI	None	None	None	None
	Zn–Cu	None	None	None	None
1,1,3-Tribromopentan-2-one	Cu–NaI	None	None	None	None
	Zn–Cu	None	40	30	None
2,6-Dibromocyclohexanone	Cu–NaI	None	40		
1,3-Dibromo-1,3-diphenylpropanone	Cu–NaI (at 80°)	None	50	80	None
1,3-Dibromo-1,3-dimethylpropanone	Cu–NaI	None	None	None	None
	Zn–Cu	None	None	70	None

Where reaction led to formation of neither cycloadduct or alkylated product, dimers produced from the oxyallyl cation were the major products—these were also present in lesser amounts when the reactions were successful.

the axial benzoate (15) as an oil in 20% yield, together with 30% recovery of unchanged alcohols and the equatorial isomer (16). This latter has yet to be separated from this mixture. Spectral data are: $\nu_{max.}$ 2 960, 2 925, 1 710, 1 600, 1 585, 1 275, and 710 cm^{-1}; $\delta(CDCl_3)$ 0.9 (6 H, d, *J* 7.5 Hz, Me), 2.4 (2 H, m, *J* 7.5, 3, and 5 Hz, C*H*Me), 4.5 (2 H, d, *J* 3 Hz, bridgehead CH), 5.5 (1 H, t, *J* 5 Hz, CHO), 6.5 (2 H, s, CH=CH), and 7.4—8.1 (5 H, m, Ph); *m/e* 258.124 9 (M^+, 3%), 136 (30), 121 (30), 105 (100), and 77 (40) ($C_{16}H_{18}O_3$ requires 258.125 6).

The compound was inactive in the primary analgetic screen.

We thank Allen and Hanburys Research Ltd. and the S.R.C. for a C.A.S.E. studentship for A. P. C.

[8/387 *Received* 2*nd March*, 1978]