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Chemistry of *gem*-Dihalocyclopropanes. XIX. Formation of 3-Oxabicyclo[3.1.0]hexane Derivatives by Intramolecular Insertion of Cyclopropylidenes

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Acetals of *gem*-dibromocyclopropanecarbaldehydes react with methyllithium at room temperature to give the corresponding derivatives of 3-oxabicyclo[3.1.0]hexane in good yields. These products result most probably from insertion of intermediate cyclopropylidenes into 5,6-related CH bonds adjacent to oxygen. A significant degree of stereoselectivity is observed. Small amounts of acetals of monobromocyclopropanecarbaldehydes are formed as well, and traces of allenes were detected in two of the reactions. Products derived from insertion into 1,3-related CH bonds adjacent to oxygen were not encountered. The regioselectivity is explained in terms of the coordinating effect of the oxygen atoms.

The intramolecular insertion reaction of cyclopropylidenes, generated from *gem*-dibromocyclopropanes and alkyllithium, may be influenced by the presence of heteroatoms in the molecule. In monocyclic ethers,[1,2] sulfides [3,4] and amines [5] of the general structure *1* insertion occurs exclusively at the CH bond adjacent to the heteroatom and 5,6-related to the electron deficient carbon (1,5-insertion) to give compounds *2*; compounds having available for insertion only 1,3-related CH bonds (1,3-insertion) preferred other reactions *e.g.* ring-opening to allenes. On the other hand, primary *gem*-dibromocyclopropanecarbinols (*1*, X=O, R=H) reacted with methyllithium to products derived from intermediate bicyclo[1.1.0]butanolates resulting from 1,3-insertion.[2]

Previous results indicate that carbenes may insert into acetal CH bonds.[6] A few *gem*-dibromocyclopropanes containing acetal functions have been treated with alkyllithium,[7–10] but 1,3-insertion into a CH bond adjacent to oxygen was structurally feasible in only three cases. In the first example [8] it was observed that allenes were not formed, but the products of this reaction were not described. In the two other examples,[9,10] the corresponding monobromides were obtained in high yields as the only product. We decided to investigate reactions of acetals of the general structure *3* with methyllithium hoping for 1,3-insertion to give the acetals of the highly interesting bicyclo[1.1.0]butanones. The results of this study are reported here.

RESULTS

The acetals *3* were prepared in 76–84 % yields from the corresponding carbonyl compounds [11,12] by conventional methods.[13] Reactions with methyllithium were carried out by adding the organometallic reagent to an ethereal solution of the acetal kept at −78 °C followed by a reaction period of several hours at room temperature. The crude reaction mixture was in each case analyzed by gas liquid chromatography (GLC) and spectroscopy. The products were isolated by distillation and when necessary by preparative GLC. Distillations were accompanied by polymerization to some extent and the product compositions refer to GLC analyses of the crude reaction mixtures.

The IR spectra of the crude products from acetals *3c* and *3d* exhibited weak bands at 1965 cm^{-1} indicating that allenes were present, but the

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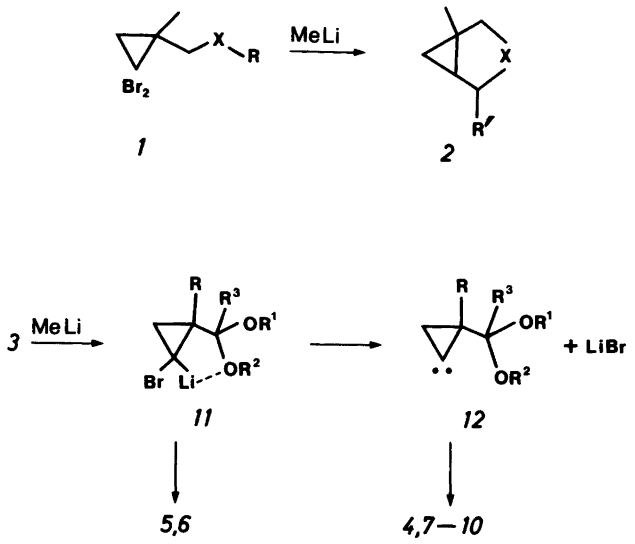
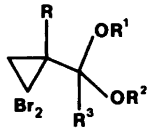


Scheme 1.

Table 1. Volatile products from reactions of acetals *3* with methyllithium.



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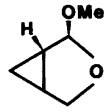
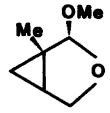
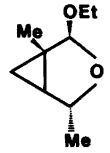
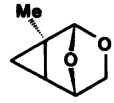
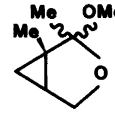
a R=R³=H,R¹=R²=Me

b R=R¹=R²=Me,R³=H

c R=Me,R¹=R²=Et,R³=H

d R=Me,R¹=R²=$-CH_2-CH_2-$,R³=H

e R=R¹=R²=R³=Me

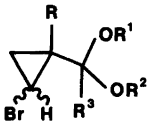
PRODUCTS	YIELDS %
 *4*	66
 *7*	73
 *8*	66
 *9*	81
 *10*	75

amounts were too small for separation by preparative GLC. The major products obtained from the reactions are recorded in Table 1. These were all isolated by distillation. In addition, small amounts of monobromocyclopropane derivatives were formed. The compounds were characterized on the basis of spectroscopic data, particularly the NMR spectra. Analyses by GLC indicated that the products recorded in Table 1 were mixtures of stereoisomers which were not separable on a preparative scale. The structural assignments had to rely on spectra recorded on the mixtures, but this did not complicate the interpretation significantly since each mixture contained 90 % or more of one isomer.

The reaction product from *3a* consisted of a mixture of four compounds in a ratio of 30:3:3:1. The first two of these, which also were the most volatile, were shown to be the stereoisomeric 2-methoxy-3-oxabicyclo[3.1.0]hexanes (*4*). Since very little spectral information on this type of compounds was available, the stereochemical assignment was not straight forward. The ^{1}H NMR spectrum of the parent compound 3-oxabiyclo[3.1.0]hexane was known [14] and surprisingly the methylene protons adjacent to oxygen are only slightly coupled to the cyclopropyl methine proton. According to the microwave spectra, both 3-oxabicyclo[3.1.0]hexane [15] and bicyclo[3.1.0]hexane [16] strongly prefer boat conformations and the replacement of the methylene group with oxygen gives rise to only minor conformational changes. This is significant since a large number of bicyclo[3.1.0]hexane derivatives have been thoroughly studied by ^{1}H NMR [17] and a comparison of these data with those of our products (Table 1) is then justified. Important in this respect is the general observation in the bicyclo[3.1.0]hexane series of a weak coupling (3–5 Hz) between the *exo* proton at C–2 and the cyclopropyl methine proton while the *endo* proton does not couple. Furthermore, the former resonates at a lower field than the latter. The acetal proton of the major isomer of *4* appears as a sharp singlet at δ 4.60 and based on the information above we assign to it the *endo* configuration, *i.e.* the methoxy group is *anti* to the cyclopropane ring.

The minor higher-boiling components of the product mixture were obtained sufficiently pure for identification. The most abundant of them was shown to be the monobromide *5a*, and the appearance of the proton adjacent to bromine as a multiplet centered at δ 2.83 may suggest a *cis* configuration.[18] The other compound was identified as one of the stereoisomers of 2-bromo-2-methylcyclopropanecarbaldehyde dimethylacetal (*6a*); the methyl group adjacent to bromine gives rise to a resonance at δ 1.72 characteristic for such compounds.[19]

The major product from the reaction of *3b* was shown to consist of a 12:1 mixture of stereoisomeric 2-methoxy-1-methyl-3-oxabicyclo[3.1.0]hexane (*7*); the acetal protons of the major and minor isomers appear as singlets at δ 4.59 and 4.80, respectively, suggesting the *exo* configuration for the former. Support for this assignment was provided by the observation of a strong nuclear Overhauser enhancement of the resonance at δ 4.59 of the major isomer when the *endo* cyclopropyl proton at C–6 was irradiated to saturation. Two minor higher-boiling products were formed in this reaction as well, but we were unable to obtain pure samples. The GLC retention times suggest they are the monobromides *5b* and *6b*.



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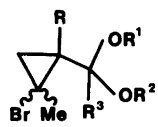

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The major product from the reaction of *3c* consisted of a 9:1 mixture of stereoisomeric 1,4-dimethyl-2-ethoxy-3-oxabicyclo[3.1.0]hexanes (*8*). The ^{1}H NMR spectrum reveals that the proton at C–4 is coupled to the adjacent cyclopropyl methine proton with J=2.9 Hz. It strongly suggests a *syn* relationship between the methyl group at C–4 and the cyclopropane ring. Furthermore, the acetal proton is present as a singlet at δ 4.54 and, by analogy,[17] the chemical shift is in accordance with an *endo* proton. Hence, we assign the *exo*-2-ethoxy, *endo*-4-methyl configuration to the major isomer. A small amount of a third compound was present in the crude product, but not sufficient for isolation; the GLC retention time indicates again that the compound is a monobromide.

The reaction of *3d* gave essentially one stereoisomer of 2-methyl-7,8-dioxatricyclo-

[3.2.1.$0^{2,4}$]octane (*9*). Only negligible coupling is observed between the protons of C-4 and C-5 in the ^{1}H NMR spectrum of *9*. In the related ether 8-oxatricyclo[3.2.1.$0^{2,4}$]oct-6-ene [20] the same protons are coupled (J=6.0 Hz) only in the *endo* isomer, while in the case of tricyclo[3.2.1.$0^{2,4}$]-octane these protons are coupled very weakly in both isomers. Hence, we cannot assign the stereochemistry of *9* on the basis of the proton coupling data alone. However, the observed shielding effects of oxygen and methylene bridges in the ^{13}C NMR spectra of norbornane derivatives [21] appear to be quite similar. Consequently we expected the cyclopropyl methylene group of *exo-9* to show an upfield shift compared with that of norcarane, while the opposite should be true for the *endo* isomer. This particular carbon resonance of *9* appears at δ 7.9, as compared with δ 10.5. for norcarane.[22] We thus favour the *exo* configuration for *9*. A small amount of higher-boiling material was also formed. When the reaction temperature was kept at −78 °C during the entire reaction period this material became practically the sole product. It was isolated in 91 % yield and identified as a 6:1 mixture of stereoisomeric 2-bromo-1-methylcyclopropanecarbaldehyde ethyleneacetal (*5d*). Based on the chemical shift of the proton adjacent to bromine the major isomer has the *trans* configuration.[18]

The product from *3e* consisted mainly of 2-methoxy-1,2-dimethyl-3-oxabicyclo[3.1.0]hexane (*10*) as a 10:1 mixture of stereoisomers. Regarding the configurational assignment the available spectral data are inconclusive.

DISCUSSION

Reactions of *gem*-dibromocyclopropane derivatives and methyllithium proceed by rapid bromine lithium exchange forming the respective α-bromocyclopropyllithium intermediate *11* (Scheme 1). Subsequently *11* eliminates lithium bromide producing a second intermediate *12* with carbene-like properties which for simplicity is regarded as a cyclopropylidene. Without stabilizing substituents *11* is converted to *12* even at −100 °C, and at −78 °C products derived from the carbene will be observed only. However, the stabilizing effect on intermediates like *11* by neighbouring oxygen atoms has been amply demonstrated [23] and it is not surprising that the monobromides, which derive from *11*, were observed in the present reactions, particularly at low temperature. More interesting, however, is the quite selective intramolecular 1,5-insertion of the cyclopropylidenes. In the present study it is practically the sole reaction of this intermediate, while ring opening to allenes was a significant path in similar reactions of ethers, amines and sulfides. Our results substantiate the notion that intramolecular 1,3-insertion into CH bonds adjacent to heteroatoms is not a favoured reaction of cyclopropylidenes. The apparent 1,5-selectivity must be attributed to the intramolecular coordinating effect of the heteroatoms with the lithium atom of *11*. The effect will probably cause *11* to attain a conformation that brings the prospective electron deficient carbon and the 5,6-related CH bond in close proximity; conversely, the 1,3-related hydrogen will point away from the said carbon, reducing the probability of insertion at that position. A prerequisite for the validity of this explanation is that insertion follows elimination of lithium bromide before significant conformational changes occur. In this connection the preference for intramolecular 1,5-insertion in arylcarbenes observed by Crow and McNab [24] is of considerable interest.

Further studies on the insertion reaction directed towards its use in synthesis are in progress.

EXPERIMENTAL

NMR spectra were recorded on Varian EM 360 A, Jeol JNM FX60 and Brucker WM-400 spectrometers.

Starting materials. The acetals were prepared from the respective carbonyl compounds [12,13] by conventional methods.[13]

2,2-Dibromocyclopropanecarbaldehyde dimethylacetal (3a), b.p. 86−88 °C (9 mmHg), 77 % yield; *2,2-dibromo-1-methylcyclopropanecarbaldehyde dimethylacetal (3b)*, b.p. 46−48 °C (0.45 mmHg), 78 % yield; *2,2-dibromo-1-methylcyclopropanecarbaldehyde diethylacetal (3c)*, b.p. 64−65 °C (0.01 mmHg), 76 % yield; *2,2-dibromo-1-methylcyclopropanecarbaldehyde diethyleneacetal (3d)*, b.p. 70−72 °C (0.01 mmHg), 79 % yield; *1-acetyl-2,2-dibromo-1-methylcyclopropane dimethylketal (3e)*, 69−70 °C (0.4 mmHg), 84 % yield.

The compounds exhibited spectral data in accordance with the assigned structures.

Reactions with methyllithium. General method. To a stirred solution of the acetal (10 mmol) in 25 ml of dry ether, kept at −78 °C, methyllithium (12 mmol, 1.5 M solution in ether) was added dropwise. After 1 h at this temperature the reaction mixture was stirred at room temperature for 6–18 h. Water was added, the ether layer separated and washed with brine. The extract was dried ($MgSO_4$) and analyzed by GLC. Subsequently the products were isolated by distillation and/or preparative GLC.

Reaction of 3a *with methyllithium.* Distillation of the crude product gave 2-methoxy-3-oxabicyclo[3.1.0]hexane (*4*), as a mixture of stereoisomers, b.p. 50–51 °C (25 mmHg). Partial decomposition occurred during distillation. *exo-4* (major isomer): ^{1}H NMR (CCl_4) δ 0.1–0.6 (2H, compl. abs.) 1.53 (2H, dq) 3.23 (3H, s), 3.70 (2H, AB J=8 Hz), 4.60 (1H, s); ^{13}C NMR (CCl_4) δ 6.5 (cyclopropyl CH_2), 14.8, 21.3 (cyclopropyl CH), 53.8 (OCH_3), 67.0 (OCH_2), 104.9 (O–CH–O).

Distillation gave also a small amount of 2-bromocyclopropanecarbaldehyde dimethylacetal (*5a*), as a mixture of stereoisomers; b.p. 70–72 °C (10 mmHg). ^{1}H NMR (CCl_4) δ 0.9–1.6 (3H, compl. abs.) 2.83 (1H, m) 3.22, 3.23 (6H, s) 4.42 (1H, d).

The second minor component 2-methyl-2-bromocyclopropanecarbaldehyde dimethylacetal (*6a*) was isolated by prep. GLC (2 m, SE-30, 15 %) as a mixture of stereoisomers.

^{1}H NMR (CCl_4) δ 0.6–1.6 (3H, compl. abs.) 1.72 (3H, s), 3.21 (3H, s), 3.23, 3.30 (3H, s), 4.10 (1H, d).

Reaction of 3b *with methyllithium.* Analysis of the crude product by GLC revealed that essentially four products had been formed in a ratio of 84:7:2:6, respectively. The 84:7 products had the same volatility and could be separated by distillation to give 2-methoxy-1-methyl-3-oxabicyclo-[3.1.0]hexane (*7*), b.p. 57–59 °C (40 mmHg). The NMR and IR spectras were recorded on this mixture. In the NMR spectra the minor isomer appears as satellites to the major resonance peaks. The 2 % and 6 % products had nearly the same retention times on GLC as the monobromides *5a* and *6a*. Attempted isolation by preparative GLC was unsuccessful.

Exo-7 (major isomer): ^{1}H NMR ($CDCl_3$) 0.42 (2H, d, J=5 Hz), 1.26 (3H, s), 1.35 (1H, d, J=5 Hz), 3.35 (3H, s), 3.38–4.05 (2H, m), 4.59 (1H, s). ^{13}C NMR ($CDCl_3$) 14.45 (cycloprop. CH_2), 14.64 ($-CH_3$), 21.98 (cycloprop. CH), 27.32 (cycloprop. C), 54.68 (CH_3-O), 67.95 ($-CH_2-O$), 106.86 (O–CH–O).

The ^{13}C NMR spectrum was sufficiently resolved in the down field part to get the resonances of *endo-7*; in the ^{1}H NMR spectrum only the acetal proton at δ 4.80 was clearly resolved. ^{13}C NMR ($CDCl_3$) δ 57.4 (CH_3O), 68.1 (CH_2O), 110.0 (OCHO).

Reaction of 3c *with methyllithium.* Distillation gave a stereoisomeric mixture of 1,4-dimethyl-2-ethoxy-3-oxabicyclo[3.1.0]hexane (*8*) b.p. 51–52 °C (9 mmHg). Major isomer: ^{1}H NMR (CCl_4) δ 0.33 (1H, q), 0.55 (1H, t, J=4.3 Hz), 1.15–1.4 (10H, compl. abs.), 3.3–3.9 (2H, compl. abs.), 4.25 (1H, dq, J=2.9 and 6.0 Hz), 4.54 (1H, s). ^{13}C NMR (CCl_4) δ 11.00 (cycloprop. CH_2), 14.90, 17.34, 30.12 (CH_3), 15.28 (cycloprop. CH), 27.30 (cycloprop. C), 62.03 (CH_2-O) 72.43 (CH–O), 105.10 (O–CH–O).

The minor isomer exhibited a singlet at δ 4.78 due to the acetal proton. The other signals were not clearly resolved.

Reaction of 3d *with methyllithium.* Analysis of the reaction product by GLC revealed that essentially one product was present and distillation afforded 2-methyl-7,8-dioxatricyclo-[3.2.1.0^{2,4}]octane (*9*), b.p. 42–43 °C (7 mmHg); ^{1}H NMR ($CDCl_3$) δ 0.02 (1H, m), 0.60 (2H, m), 1.27 (3H, s), 3.47 (2H, d, J=1.5 Hz), 4.57 (1H, br.s), 5.23 (1H, s); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 7.9 (cyclopropyl CH_2), 13.6 (CH_3), 18.9 (cyclopropyl CH), 23.4 (cyclopropyl C), 67.6 (CH_2O), 76.8 (O–CH), 103.7 (O–CH–O).

When the reaction was carried out by stirring the reaction mixture at −78 °C for 1 h, before decomposing with water, *9* was not formed; distillation gave 2-bromo-1-methylcyclopropanecarbaldehyde ethyleneacetal (*5d*) in 91 % yield, b.p. 85–86 °C (9 mmHg) as a mixture of stereoisomers in a ratio of 6:1; ^{1}H NMR (CCl_4) δ 0.58 (1H, q, J=4 Hz) 1.28 (3H, s) 1.28 (1H, m) 3.02 (1H, q, J=4 Hz) 3.83 (4H, m) 4.63 (1H, s); ^{13}C NMR (CCl_4) δ 16.8 (CH_3) 18.5 (cyclopropyl CH_2) 24.5 (cyclopropyl C) 31.8 (CHBr) 64.7 (CH_2O) 104.9 (O–CH–O).

Reaction of 3e *with methyllithium.* Distillation of the product gave 2-methoxy-1,2-dimethyl-3-oxabicyclo[3.1.0]hexane (*10*) as a mixture of stereoisomers, b.p. 48–50 °C (18 mmHg); ^{1}H NMR (CCl_4) δ 0.28 (1H, br. s), 0.37 (1H, s), 1.17 (3H, s), 1.2 (1H, m), 1.23 (3H, s), 3.13 (3H, s), 3.62 (2H, ABX J_{AB}=7.5 Hz J_{AX}=2 Hz), ^{13}C NMR (CCl_4) δ 14.6 (cyclopropyl CH_2), 14.6, 16.4 (CH_3), 22.9 (cyclopropyl CH), 31.3 (cyclopropyl C), 47.8 (OCH_3), 67.0 (OCH_2), 106.9 (O–CH–O).

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