On the Reactivity of (7-Oxabicyclo[2.2.1]hept-5-en-2-ylidene)amines. Different Reaction Paths Leading to the Same Final Products

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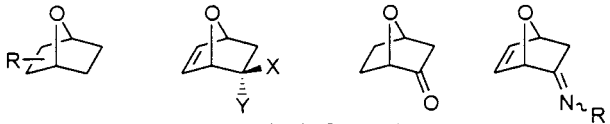
Dedicated to Prof. *André M. Braun* on the occasion of his 60th birthday

The reaction of amines, *N*-substituted by a 7-oxabicyclo[2.2.1]hept-5-en-2-ylidene moiety, either with PhSCl or *m*CPBA (*meta*-chloroperbenzoic acid) unexpectedly afforded the same type of furan derivatives by two different reaction paths. The results confirm the intervention of a homoconjugative, electron-releasing effect of the oxabicycloalkenylideneamine moieties, as predicted theoretically.

1. Introduction. – Substituted 7-oxabicyclo[2.2.1]heptane derivatives **1** are important synthetic intermediates because these compounds show a broad spectrum of reactivity generally in a predictable regio- and stereocontrolled fashion [1]. In particular, remote controlled electrophilic addition to the endocyclic C=C bond of the unsaturated derivatives **2**[1]) [2][3] and nucleophilic addition to the carbonyl group of compounds **3**[2]) [4] have been considered in depth.



1 **2a** X = CN, Y = AcO **3** **4**

b X, Y = O

c X, Y = R^1O

d X = R^2O, Y = R^1

e X = R^1, Y = R^2O

To the best of our knowledge, the reactivity of alkylideneamines (= formal *N*-substituted imines) derived from 7-oxatrinorbornene **4** [5] has not been previously reported, perhaps because the *a priori* expected pattern of reactivity for these compounds should not be very different that observed for their precursor **2b**. However, the very different behavior shown by compounds **4** as compared with ketone **2b** in two well-known and synthetically useful reactions constitutes a not-yet-reported aspect of the chemistry of these bicyclic systems, which is the object of the present report.

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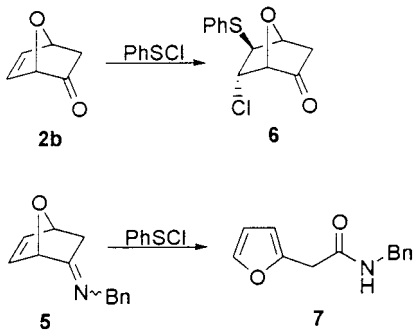
[1]) For studies on remote substituent effects in bicyclic systems, see *e.g.* [2]; for synthetic applications, see *e.g.* [3].

[2]) For the stereochemical control of nucleophilic additions to bicyclic ketone **3**, see *e.g.* [4].

Quantum calculations by *Carrupt* and *Vogel* [6] have predicted that homoconjugated imino substituents can be electron-releasing-like carbonyl moieties.

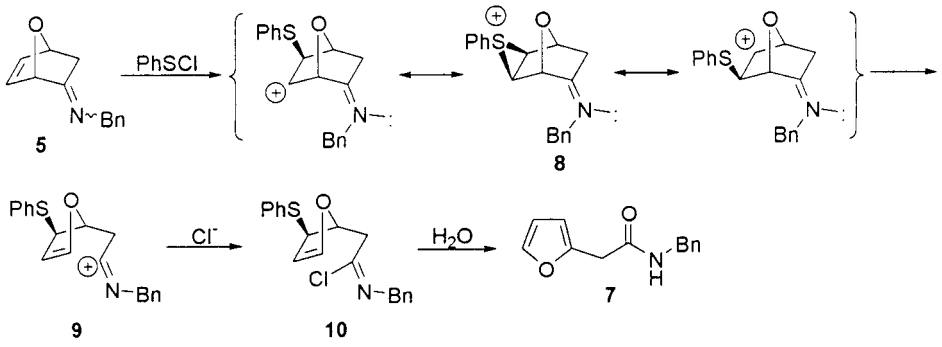
2. Results and Discussion. – 2.1. *Reaction of* N-*(7-Oxabicyclo[2.2.1]hept-5-en-2-ylidene)benzylamine* (**5**) *with Phenylsulfonyl Chloride.* The 7-oxatrinorbornenone **2b** reacts with PhSCl to give the 5-*exo*-(phenylsulfenyl)-6-*endo*-chloro derivative **6** in a reaction in which the remote carbonyl group behaves as a homoconjugated electron-donating group [7] (*Scheme 1*). Under the same reaction conditions, alkylideneamine **5** gave the furan derivative **7**. No traces of the expected addition product to the endocyclic C=C bond were observed.

Scheme 1



To account for this result, a *Grob* fragmentation [8] with C(1)–C(2) σ-bond cleavage of the bicyclic system can be proposed[3]) [9][10] (*Scheme 2*). Thus, the expected episulfonium ion intermediate **8** undergoes σ(C(1)–C(2)) bond fragmentation to give nitrilium ion **9**, which, after being captured by the Cl^- counterion, affords the imidoyl chloride **10**. Hydrolysis of **10** [11] followed by aromatization under workup of the reaction crude yields amide **7**.

Scheme 2

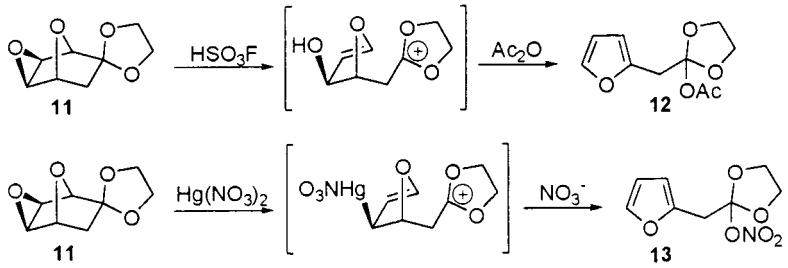


[3]) For synthetic applications of the *Grob* fragmentation, see [9]; for a discussion on the aza-*Grob* fragmentation, see [10].

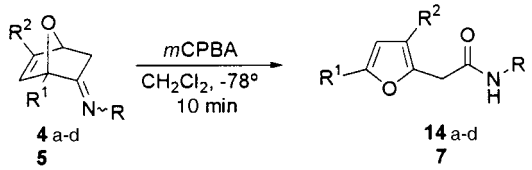
Two aspects should be pointed out regarding the proposed reaction path: first, oxatrinorbornenone-derived ketals such as **11** have been found to be transformed into furan derivatives by treatment with fluorosulfonic acid (transformation of **11** into **12**) [12] or $Hg(NO_3)_2$ in MeCN (transformation of **11** into **13**) [13][14] (*Scheme 3*)[4]). Second, the alignment of the n(N) orbital with the σ(C(1)–C(2)) bond (case of the (*Z*)-isomer of **5**) is probably the reason for the ease of the fragmentation as predicted by *Carrupt* and *Vogel* [6]. The MM2 [5] and PM3 calculations performed on (*Z*)-**5** indicate an almost perfect alignment of the σ(C(1)–C(2)) and n(N) orbitals. Thus, the (*Z*)-diastereoisomer should be the reactive one, according to the stereoelectronic requirements of the *Grob* fragmentation [8]. The equilibrium (*E*)-**5** ⇄ (*Z*)-**5** (15 : 1 in the starting material) is shifted with the consumption of the more reactive (*Z*)-**5** diastereoisomer.

2.2. *Reactions of* N-*(7-Oxabicyclo[2.2.1]hept-5-en-2-ylidene)amines* **4** *and* **5** *with* meta-*Chloroperbenzoic Acid* (*m*CPBA). Amines **4** and **5** react with *m*CPBA (CH_2Cl_2, –78°, 10 min) to give the amides **14** and **7**, respectively (*Scheme 4*).

Scheme 3



Scheme 4

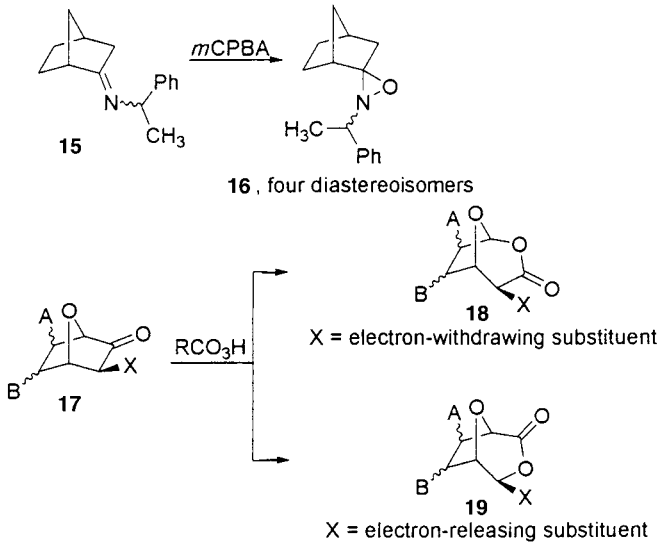


	R	R^1	R^2	Product (%)[a])
5	$PhCH_2$	H	H	**7** (90)
4a	PhCH(Me)	H	H	**14a** (90)
b	CH_2=CH–CH_2	H	H	**b** (85)
c	$PhCH_2$	H	Br	**c** (70)
d	CH_2=CH–CH_2	Me	H	**d** (75)

[a]) Isolated yield

[4]) For other examples of *Grob* fragmentations involving 7-oxabicyclo[2.2.1]heptane systems, see [1a][14].

Scheme 5



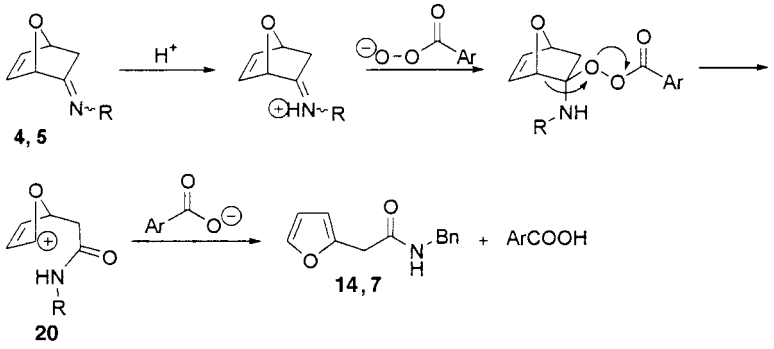
It should be noted that the reaction of the alkylideneamines derived from trinorcamphor **15** with *m*CPBA has been previously reported to afford the expected oxaziridines **16** as a mixture of diastereoisomers [15]. On the other hand, 7-oxatrinorbornanones such as **17** react with *m*CPBA to give the products of the *Baeyer-Villiger* lactonization **18** or **19** [16] (*Scheme 5*). In our hands, 7-oxatrinorbornenone **2b** did not react with *m*CPBA under the conditions indicated for the reactions in *Scheme 5*. Thus, the simultaneous presence of the endocyclic double bond and of the alkylideneamino functionality appears to be responsible for the observed transformation.

A probable reaction path for the transformation depicted in *Scheme 4* is outlined in *Scheme 6*. Thus, in this case, the endocyclic C=C bond in **4** and **5** seems to induce the generation of an allylic cation **20** *via* σ(C(1)–C(2)) fragmentation. Proton abstraction (probably by reaction with the carboxylate anion) yields the observed products **14a–d** and **7**. It is worth mentioning that this reaction path reminds that proposed for the *Beckmann* fragmentation in dehydrotrinorcamphor oximes [17].

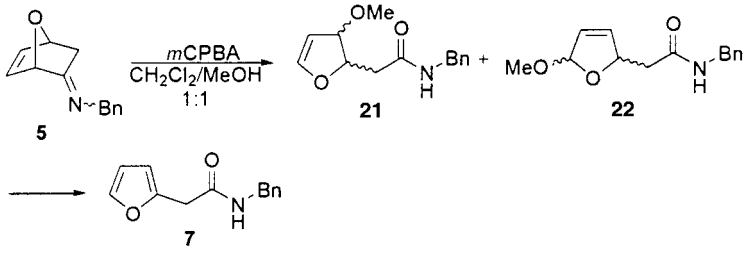
The trapping of the cationic intermediate **20** was achieved by reaction of **5** with *m*CPBA in CH_2Cl_2/MeOH 1:1. Under these conditions, a *ca.* 1:1 mixture of the dihydrofuranacetamides **21** and **22** was observed and characterized (^{1}H-NMR). This mixture evolved smoothly to the furan derivative **7** (*Scheme 7*).

Conclusion. – We described the unexpected behavior of alkylideneamines derived from 7-oxatrinorbornenone in two different reactions giving rise, through two different reaction paths, to the same type of furan derivatives. The results reported herein open the way for further research in the almost unexplored chemistry of the oxatrinorbornenylideneamines and related *N*-derivatives.

Scheme 6



Scheme 7



Experimental Part

General. TLC: silica gel *60* F_{254}; detection by UV light and vainilline soln. Flash column chromatography (FC): silica gel *60*. $[\alpha]_D$: $CHCl_3$ soln. at 25°. IR Spectra: $CHCl_3$ solns. in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: at 300 and 75.5 MHz, resp.; $CDCl_3$ solns. δ in ppm rel. to $SiMe_4$ (= 0 ppm), J in Hz.

Reaction of N-*(7-Oxabicyclo[2.2.1]hept-5-en-2-ylidene)benzylamine* (**5**) *with Phenylsulfonyl Chloride.* To a soln. of *N*-chlorosuccinimide (66 mg, 0.50 mmol) in $CHCl_3$ (0.5 ml) at 0°, PhSH (0.05 ml, 0.50 mmol) was added, and the mixture was stirred for 30 min. Amine **5** (50 mg, 0.25 mmol) in $CHCl_3$ (1.25 ml) was added and the mixture stirred at 0° for 1 h and at r.t. for 18 h. The mixture was quenched with 5% $NaHCO_3$ soln. (1 ml) and extracted with CH_2Cl_2 (3 × 2 ml). The combined org. extracts were washed with brine (1 × 2 ml), dried ($MgSO_4$), and evaporated: pale yellow oil, which was purified by FC (AcOEt/hexane 1:1).

Reactions of N-*(7-Oxabicyclo[2.2.1]hept-5-en-2-ylidene)amines* **4** *and* **5** *with* meta-*Chloroperbenzoic Acid: General Procedure.* A soln. of **4** or **5** (0.5 mmol) in CH_2Cl_2 (1.25 ml) was added dropwise to a suspension of *m*CPBA (0.6 mmol) in CH_2Cl_2 (3.6 ml) at −78°. After 10 min, sat. $Na_2S_2O_3$ soln. (2 ml) was added, and the mixture was allowed to warm to r.t. The org. phase was washed with brine (2 ml), dried ($MgSO_4$), and evaporated: pale yellow oil, which was purified by CC (AcOEt/hexane 1:1).

N-*Benzylfuran-2-acetamide* (**7**). White solid. M.p. 55–58° (hexane/AcOEt). IR: 3490, 1715, 1680. ^1H-NMR: 7.50 (*d*, ^3J = 1.8, 1 H); 7.40–7.20 (*m*, 5 H); 6.38 (*dd*, ^3J = 3.0, 1.8, 1 H); 6.25 (*d*, ^3J = 3.2, 1 H); 6.00 (*s*, NH); 4.70 (*d*, ^3J = 5.6, 2 H); 3.68 (*s*, 2 H). ^{13}C-NMR: 168.4; 148.4; 142.4; 137.8; 128.5; 127.3; 110.7; 108.5; 43.5; 36.1. Anal. calc. for $C_{13}H_{13}NO_2$: C 72.54, H 6.09, N 6.51; found: C 72.63, H 6.12, N 6.60.

N-*[(1R)-1-Phenylethyl]furan-2-acetamide* (**14a**). Colorless oil. $[\alpha]_D^{25}$ = 8.9 ($CHCl_3$, *c* = 2). IR: 3495, 1710, 1680. ^1H-NMR: 7.35 (*d*, ^3J = 1.2, 1 H); 7.25–7.10 (*m*, 5 H); 6.30 (*dd*, ^3J = 3.1, 1.9, 1 H); 6.15 (*d*, ^3J = 3.2, 1 H); 5.90 (br. *s*, NH); 5.05 (*m*, 1 H); 3.55 (*s*, 2 H); 1.40 (*d*, ^3J = 7.0, 3 H). ^{13}C-NMR: 167.7; 148.8; 143.0; 142.5; 128.7; 127.4; 126.1; 110.9; 108.6; 48.9; 36.4; 21.9. Anal. calc. for $C_{14}H_{15}NO_2$: C 73.34, H 6.59, N 6.11; found: C 73.42, H 6.60, N 6.25.

N-*(Prop-2-enyl)furan-2-acetamide* (**14b**). Colorless oil. IR: 3490, 1715. ^1H-NMR: 7.35 (*d*, ^3J = 1.6, 1 H); 6.30 (*dd*, ^3J = 3.2, 1.6, 1 H); 6.15 (*d*, ^3J = 3.2, 1 H); 5.85–5.55 (*m*, =CH, NH); 5.05 (*dd*, ^3J = 19.1, 10.3, 2 H); 3.80

(*t*, $^3J = 5.6$, 2 H); 3.55 (*s*, 2 H). ^{13}C-NMR: 168.6; 148.6; 142.5; 133.8; 116.2; 110.8; 108.7; 41.9, 36.2. Anal. calc. for $C_9H_{11}NO_2$: C 65.44, H 6.71, N 8.48; found: C 65.59, H 6.83, N 8.66.

N-*Benzyl-3-bromofuran-2-acetamide* (**14c**). White solid. M.p. 115–117° (hexane/AcOEt). IR: 3490, 1710, 1685. ^{1}H-NMR: 7.30 (*d*, $^3J = 2.1$, 1 H); 7.25–7.10 (*m*, 5 H); 6.38 (*d*, $^3J = 2.1$, 1 H); 5.75 (br. *s*, NH); 4.40 (*d*, $^3J = 5.7$, 2 H); 3.65 (*s*, 2 H). ^{13}C-NMR: 167.6; 146.6; 143.3; 138.2; 128.0; 127.9; 114.6; 99.8; 44.1; 34.8. Anal. calc. for $C_{13}H_{12}BrNO_2$: C 53.08, H 4.11, N 4.76; found: C 53.19, H 4.30, N 4.90.

5-Methyl-N-*(prop-2-enyl)furan-2-acetamide* (**14d**). Colorless oil. IR: 3495, 1710. ^{1}H-NMR: 6.05 (*d*, $^3J = 3.0$, 1 H); 5.90 (*d*, $^3J = 2.5$, 2 H); 5.85–5.60 (*m*, =CH, NH); 5.05 (*dd*, $^3J = 19.2$, 10.0, 2 H); 3.80 (*t*, $^3J = 5.6$, 2 H); 3.55 (*s*, 2 H); 2.15 (*s*, 3 H). ^{13}C-NMR: 166.8; 152.2; 146.7; 133.9; 115.9; 109.4; 106.5; 41.8; 36.3; 13.4. Anal. calc. for $C_{10}H_{13}NO_2$: C 67.02, H 7.31, N 7.82; found: C 67.15, H 7.11, N 7.61.

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