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PERIPHERAL CONJUGATE SYSTEMS 1. CYCLOADDITION OF INDOLIZINE TO ELECTRON-DEFICIENT OLEFIN

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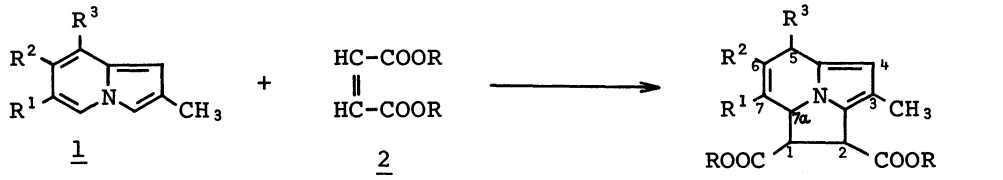
Indolizines reacted with esters of maleic and acrylic acid to give 1,2,5,7a-tetrahydropyrrolo[2,1,5-cd]indolizine derivatives which would be presumably derived from [8+2] cycloaddition and subsequent 1,5-hydrogen shift, while with maleimide and maleic anhydride were obtained Michael adducts as main products. The stereochemistry and mechanism of the reactions were also discussed.

Indolizine is a heterocycle which contains eight π-electrons in the perimeter (excepting two n-electrons on the condensed nitrogen atom) and in which both termini of the conjugated system are fixed in convenient positions to cycloaddition reaction. Boekelheide and his co-workers[1] have provided a favorable method for the synthesis of cycl[3.2.2]azine derivatives using this compound in the reaction with dimethyl acetylenedicarboxylate. The details, however, remain unexplained since the above reaction has been carried out under dehydrogenating conditions.

In this letter, the authors wish to communicate [8+2] cycloaddition reactions, accompanied by [1,5] sigmatropic hydrogen shift, of indolizines 1 with such electron-deficient olefins as maleates 2, acrylate 3, maleic anhydride 4 and maleimides 5.

On heating 2-methylindolizine 1a with an equivalent amount of diethyl maleate 2a in chloroform was given the product 6a which was found to be a 1:1 adduct of 1a to 2a by the mass spectrum as well as the elemental analysis. The resonances of all protons in 6a were shifted to higher field than τ3.5, but the starting 1a showed all signals for ring protons in the region below 4.0. Unfortunately, the structure of the signal arising from one methine proton was indistinct because it was obscured by the two methylene quartets due to the ester groups.



1

a; $R^1=R^2=R^3=H$
b; $R^1=CH_3$, $R^2=R^3=H$
c; $R^2=CH_3$, $R^1=R^3=H$
d; $R^3=CH_3$, $R^1=R^2=H$

2

a; $R=C_2H_5$
b; $R=CH_3$

6

a; $R=C_2H_5$, $R^1=R^2=R^3=H$
b; $R=CH_3$, $R^1=R^2=R^3=H$
c; $R=R^1=CH_3$, $R^2=R^3=H$
d; $R=R^2=CH_3$, $R^1=R^3=H$
e; $R=R^3=CH_3$, $R^1=R^2=H$

Accordingly, the 1:1 adduct of 1a to dimethyl maleate 2b was synthesized by the similar reaction. The PMR spectrum of this adduct 6b revealed only three olefinic protons at $\tau 3.79^{m}$, 4.00^{m} and 4.38^{s}, three methine protons at 5.86^{d} (J=7.0 Hz), 6.70^{dd} (J=7.0 and 9.5) and $4.9^{br.m}$ and two protons probably assignable to a methylene at 6.76 as a narrow multiplet (Fig. 1).

This spectrum indicates that the structure of 6b would result from migration of a methine hydrogen in the original [8+2] cycloadduct somewhere in the six-membered ring. Therefore, each methyl group was introduced at 6- or 7-position of 6b (correspond to 6d and 6c, respectively) to ascertain the location of an inconstant hydrogen. Thus, 6c and 6d were prepared from 2,6-dimethyl- 1b and 2,7-dimethylindolizine 1c with 2b, respectively. Few change in these PMR spectra was observed and both signals for methyl groups on the six-membered ring were kept as singlets as usual.

However, 3,5-dimethyl derivative 6e, prepared from 2,8-dimethylindolizine 1d with 2b in a low yield, offered an unambiguous evidence for the structure. The PMR spectrum of 6e reproduced in Fig. 1 showed the similar pattern to those of 6a-6d except that the newly introduced methyl group was observed as a doublet by coupling with a methine proton on the same carbon atom.

From the PMR spectral data summarized in Table 2, the structures of the products 6a-6e were deduced to be 1,2,5,7a-tetrahydropyrrolo[2,1,5-cd]indolizines. Double resonance experiments confirmed the individual assignments and led to determination of coupling constants.

If a configurational inversion of the central nitrogen atom does not occur, eight configuration are possible for the structure of 6. The most reasonable structure A was selected on the basis of a study of the coupling constants and an inspection of Dreiding models. In A, each hydrogen atom at 7a- and 1-position occupies

Table 1. Reactions of 1 with 2, 3, 4, and 5.

Product	Yield (%)	Mp (°C)	$\nu_{C=O}$ (cm^{-1})	M^+ (m/e)	Reaction Conditions
6a	59	64.5-66	1740	303	Reflux in chloroform for 6 hr
6b	65	107.5-108	1740	275	Reflux in chloroform for 6 hr
6c	75	121-122.5	1745	289	Reflux in chloroform for 10 hr
6d	77	114.5-115.5	1730	289	Reflux in chloroform for 10 hr
6e	5	151-152.5	1730	289	Reflux in chloroform for 6 hr
7	41	75-76	1720	-	Reflux in excess methyl acrylate for 6 hr
8	100	111-113	1860 (1800	229	Reflux in benzene for 2 hr
9a	85	60[a]	161-162	1780	-	eflux in benzene for 3 hr
10a		40[a]	-	1705	-	
9b	65	70[a]	149-150.5	1770	-	eflux in benzene for 3 hr
10b		30[a]	-	1700	-	

a) ; Relative yields were determined by the PMR spectra.

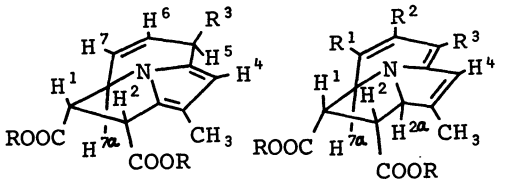
Table 2. PMR Data

	Chemical Shift in $CDCl_3$; τ								Coupling Constants; Hz	
	1-H[dd]	2-H[d]	3-CH_3[s]	4-H[s]	5-H[m]	6-H[m]	7-H[m]	7a-H[br.m]	J_{1-2}	J_{1-7a}
6a	6.67	5.80	7.91	4.31	CH_2;6.7	3.90	3.68	4.8	7.5	9.8
6b	6.70	5.86	7.92	4.38	CH_2;6.8	4.00	3.79	4.9	7.0	9.5
6c	6.47	5.77	7.94	4.37	CH_2;6.8	4.32	CH_3;8.13(s)	4.9	8.0	9.5
6d	6.67	5.84	7.91	4.37	CH_2;6.8	CH_3;8.12(s)	4.09	4.9	7.5	10.0
6e	6.57	5.79	7.89	4.32	6.6,CH_3; 8.65(d)[a]	4.16	3.81	4.9	7.3	9.9
7	b)	CH_2[b]	7.95	4.38	b)	3.96	3.88	5.3	-	-

	8b-H[t]	3a-H[d]	4-CH_3[s]	5-H[s]	6-CH_3[m]	7-H[m]	8-H[m]	8a-H[br.m]	J_{8b-3a}	J_{8a-8b}
10a	6.04	5.60	7.88	4.31	6.8	4.00	3.70	5.3	7.0	7.0
10b	6.05	5.63	7.93	4.45	6.8	4.11	3.68	5.3	7.0	7.0

	3-H[dd]	cis-4-H[dd]	trans-4-H[dd]	CH_3	aromatic protons	J_{3-c4}	J_{3-t4}	J_{c4-t4}
8	5.27	6.65	6.98	7.76	2.6-3.8	10.2	8.0	19.0
9a	5.36	6.68	7.08	7.70	2.4-3.7	9.9	6.4	18.6
9b	5.44	6.77	7.17	7.75 7.66	2.5-3.8	9.6	6.0	18.6

a) ; J=7.2 Hz, b) ; All of these protons are overlapping to one another in τ6.7-7.0.



A B

anti-periplanar and each one at 1- and 2-position syn-periplanar. A considerably small coupling constant between 6-H and 5-H in 6e (below 2 Hz) indicates that the migrated hydrogen atom (5-H) would be located cis to 7a-H. As a [1,5] sigmatropic hydrogen shift is allowed in suprafacial manner, it was concluded that the final product 6e (A; $R=R^3=CH_3$) has resulted from the exo [8+2] cycloadduct B ($R^1=R^2=H$, $R=R^3=CH_3$). In the same way, other exo [8+2] cycloadducts B might be formed as initial products from the reactions of 1 with 2 and rapidly[2] followed by hydrogen shift into the final products A (identical to 6).

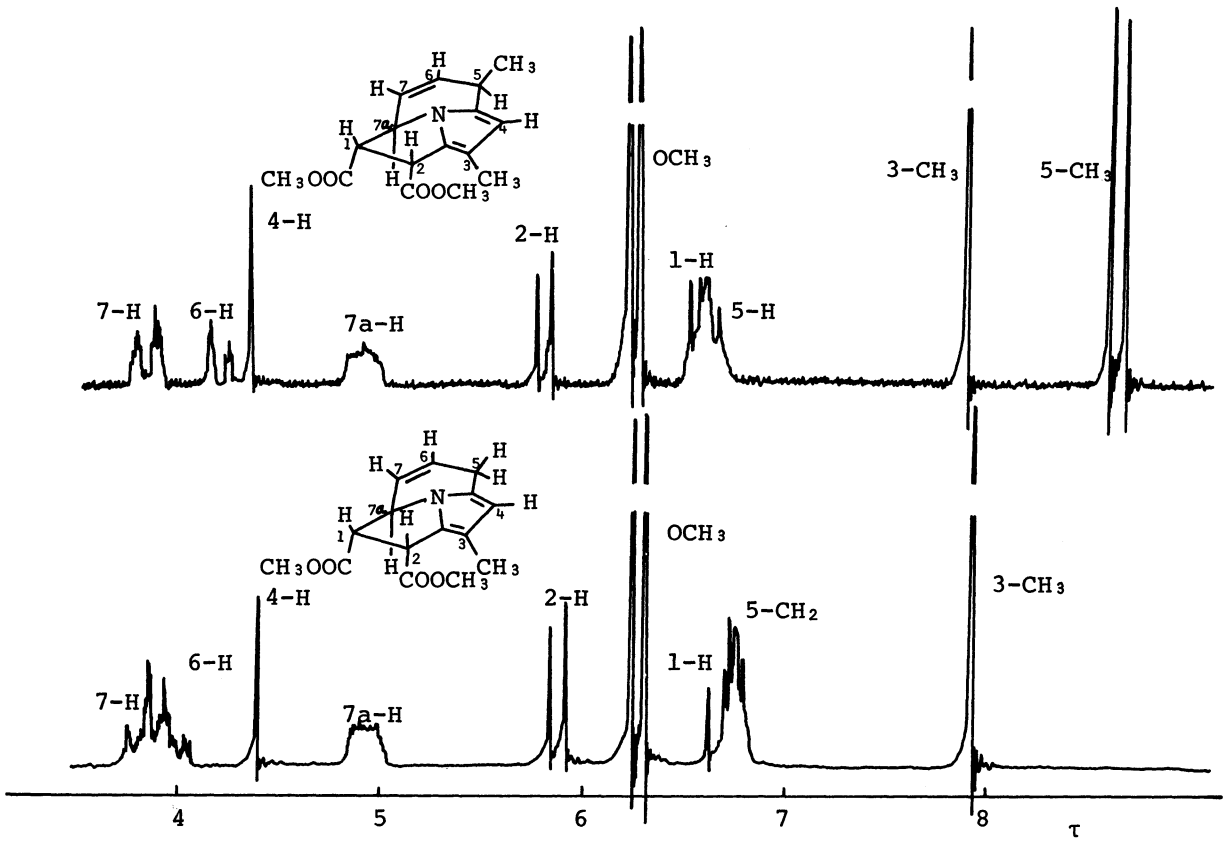
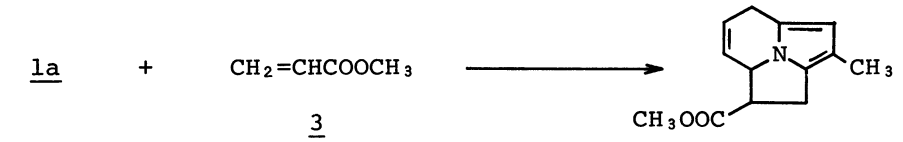


Fig. 1. Partial PMR Spectra of 6b (bottom) and 6e (top) at 100 MHz in $CDCl_3$.

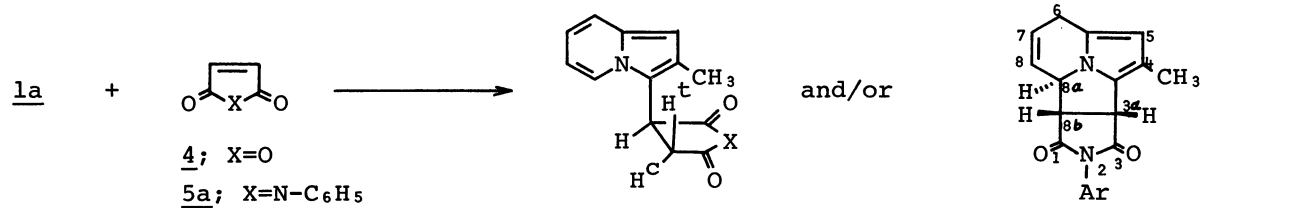
The reaction of 1a with methyl acrylate 3 gave the analogous adduct 7 whose structure was determined by the PMR spectrum (Table 2).

On the other hand, maleic anhydride 4 easily reacted with 1a affording a 1:1 adduct 8 in quantitative yield. The compound 8 was identified to be 3-indolizinylsuccinic anhydride with the aid of its PMR spectrum, in which the resonance of all ring protons closely beared resemblance to that of 1a except for an olefinic proton

at 3-position in 1a, and which exhibited three protons assignable to a methylene and a methine group in ABX pattern as shown in Table 2.



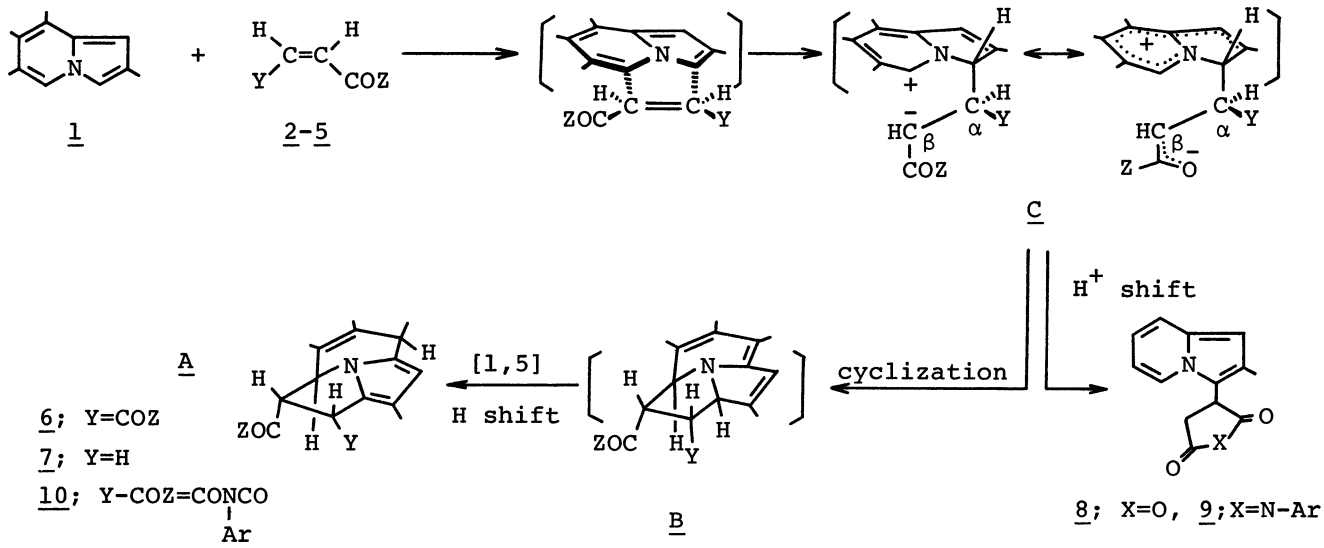
1a + CH_2=$CHCOOCH_3$ (3) → 7



1a + 4; X=O / 5a; X=N-C_6H_5 / 5b; X=N-C_6H_4-CH_3(p) → 8; X=O / 9a; X=N-C_6H_5 / 9b; X=N-C_6H_4-CH_3(p) and/or 10a; Ar=C_6H_5 / 10b; Ar=C_6H_4-CH_3(p)

The similar reactions of 1a with N-phenyl- 5a and N-p-tolylmaleimide 5b yielded the respective Michael adducts, 9a and 9b, accompanying with formation of 1H-dipyrrolo-[3,4-a:2',1',5'-cd]indolizine-1,3-diones 10a and 10b. Analysis of the coupling constants presumed that the products 10 would originate from exo [8+2] cycloadducts. However, 10a and 10b could not be isolated as a pure form because of their lability.

As mentioned above, the reactions of indolizines with the electron-deficient olefins yielded 1,2,5,7a-tetrahydropyrrolo[2,1,5-cd]indolizines produced by 1,5-hydrogen shift from the initially formed [8+2] cycloadducts in some cases, but Michael adducts in another cases. Formation of the products can be most reasonably accommodated by a stepwise mechanism started by nucleophilic attack of indolizines on electron-deficient olefins.



1 + 2-5 → C → A (6; Y=COZ / 7; Y=H / 10; Y-COZ=CONCO-Ar) [1,5] H shift ← B ← cyclization; C → H^+ shift → 8; X=O, 9; X=N-Ar

The first step involves formation of zwitterionic intermediates C derived probably via an exo-transition state[3]. In C, protonic migration of the hydrogen atom at the reaction center to β-carbon atom leads to Michael adducts 8 and 9. In contrast coupling of the both charges causes formation of exo [8+2] cycloadducts B. In contrast coupl- cyclization would proceed in a less sterically hindered manner, whether the Cα-Cβ bond in C can afford to rotate or not, to give the stereospecific [8+2] cycloadducts B and soon followed by suprafacial [1,5] sigmatropic hydrogen shift with formation of the isolated products 6, 7 and 10.

This mechanism is supported by the extraordinary sensibility of the reaction rate to the polarity of solvent. The reaction of 1a with 2b proceeded ca. 500 times faster in chloroform than in benzene[4].

REFERENCES AND NOTES

1. A. Galbraith, T. Small, R. A. Barnes, and V. Boekelheide, J. Amer. Chem. Soc., 83, 453 (1961).
2. Tracing experiments of the reaction of 1a with 2b in deuteriochloroform by using PMR spectrometer showed that no any signals assignable to the exo [8+2] cycloadduct B (R^1= R^2= R^3=H, R = CH_3) were found out during the reaction time. This indicates the initial cycloadducts B are readily converted into the final products A by 1,5-hydrogen shift as soon as B are formed.
3. According to the semi-empirical LCAO-SCF calculation of 1, the reactions of 1 with the electron-deficient olefins would favor endo-approach. The steric hindrance between indolizine nuclei and unsaturated substituents in olefins, however, might defeat the above approach to give the unexpected results.
4. The rate constant of the second-order reaction at 95.0 °C is 4.87×10^{-4} in chloroform and 1.04×10^{-6} [$l \cdot mole^{-1} \cdot sec^{-1}$] in benzene.

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