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A SIMPLE ONE-POT SYNTHESIS OF THE TRICYCLIC MITOMYCIN SKELETON.

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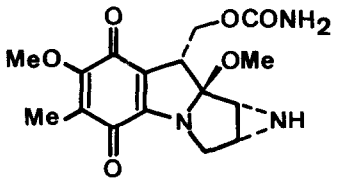
Summary. Reaction of [E,E]-hexa-2,4-dienal 2 with nitrosobenzene led regiospecifically to the Diels-Alder cycloadduct 4b which is unstable at room temperature. Its enol form 5b underwent a hetero-Cope rearrangement, giving ultimately the pyrroloindole 7b. Simultaneously base-catalyzed deprotonation of 4b gave the dicarbonyl intermediate 9b which ring-closes in two ways, leading eventually to the betaïne 11b and to small amounts of the pyrrole 10b.

Mitomycins —e.g. mitomycin A 1 — are natural products which exhibit antibiotic and antitumor activities (1-3). The rather unusual pyrroloindole structure of these compounds led several research groups to undertake their total synthesis (4). To achieve this goal Coates and Hutchins made use of an unusual hetero-Cope rearrangement, starting from an N-phenyl-O-vinylhydroxylamine derivative (5).



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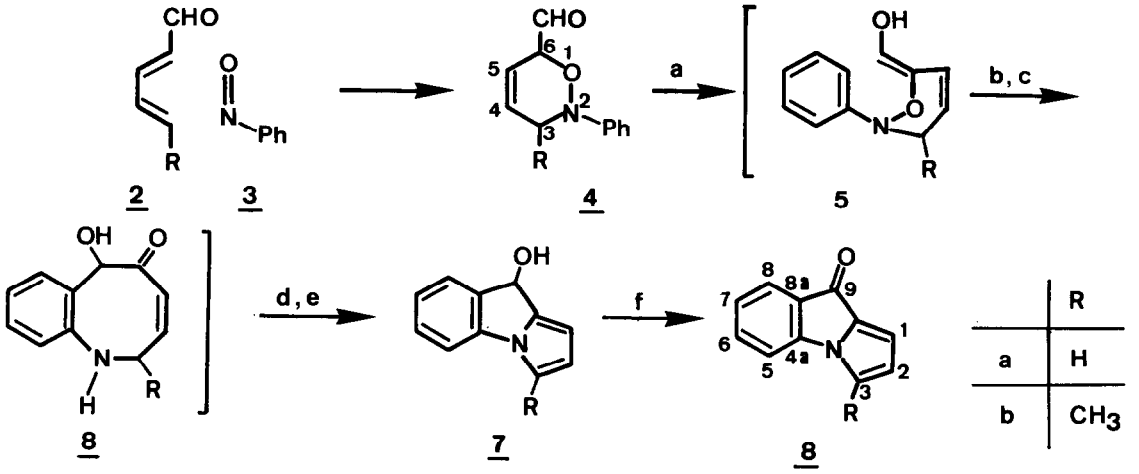
We describe herein some preliminary results which permit the synthesis —in a one-pot procedure — of the pyrroloindole alcohols 7, along with small amounts of the corresponding ketones 8. These syntheses are essentially based on a sequential combination of a hetero-Diels-Alder cycloaddition — between nitrosobenzene 3 and hexadienal 2b (or pentadienal 2a) — and of a hetero-Cope rearrangement, the latter one being akin to the Coates and Hutchinson procedure (5).

When a solution of equimolar amounts of [E,E] hexa-2,4-dienal 2b (3.3 g; 33 mmol) and of nitrosobenzene 3 in absolute ethanol was left to react under argon at 45-50°C for 2 days, the starting material disappeared. According to ^{1}H-NMR, as determined with the reaction mixture, two major products had formed in 55 % and 35 % yields respectively, along with two minor ones. After separation by column chromatography one of the two major components was shown to be the colourless tricyclic alcohol 7b (mp 158°C; 35 % ; crystallisation from toluene); the mother liquors of crystallisation were treated with MnO_2 whereby the ketone 8b formed as yellow crystals (mp 123.5 - 124°C; 11 %). The other major component was a highly polar compound (mp 180°C dec.; 35 %) which was identified with the already known betaïne 10b

(lit. mp 182 - 183°C dec.) (6). The two minor reaction products proved to be the tricyclic ketone 8b (6 %) and the 2-formylpyrrole 11b (mp 94.5° C; 1 %) (7).

Using similar experimental conditions pentadienal 2a — which was prepared from pyridine according to a known procedure (8) — reacted with 3 and led to analogous results; namely the formation of the following compounds, all of which are known :



a) Enolisation; b) hetero-Cope rearrangement; c) prototropy and aromatisation; d) intramolecular nucleophilic addition; e) elimination of a water molecule; f) oxidation with MnO_2

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the tricyclic alcohol 7a (mp 115 -116°C; lit. 116 - 118°C) (9), the corresponding yellow ketone 8a (mp 120.5 - 121°C; lit. 121 - 122°C) (10); the betaïne 10a (mp 155°C dec.; lit. 160°C dec.) (11), and the 2-formylpyrrole 11a (mp 25 -28°C; lit. 27 -30°C) (12). This reaction having been performed on a small scale, yields were not determined.

That the primary Diels-Alder cycloadduct 4 did indeed form could be demonstrated as follows. Reaction of equimolar amounts of 2b and 3 at + 15°C in C_6D_6 was monitored by ^{1}H-NMR and shown to proceed slowly, whereby 4b formed in close to quantitative yield [(C_6D_6, TMS) δ0.85 (d; Me), 3.66 (m; H-3), 5.61 (m; H-4), 5.84 (m; H-5), 4.47 (m; H-6), 9.73 (s; CHO); $J_{3\text{-Me}}$= 7.3; $J_{3,4}$= 2.5; $J_{3,5}$= 1.8; $J_{3,6}$= 2.3; $J_{4,5}$=10.1; $J_{4,6}$=2.0; $J_{5,6}$=3.0]. This spectrum proved to be very similar to the one which had been reported for the Diels-Alder adduct of methyl sorbate with 3 (13). When heated up to 50°C 4b disappeared in favour of the above described products, i.e. essentially 7b and 10b.

Spectral analyses of the newly described compounds were in good agreement, in particular with 8a (Tables 1 and 2). To make sure that the carbon-atom sequence is as indicated in 8b, ^{13}C-^{13}C coupling constants were measured (Table 3) : they demonstrate that the proposed structure 8b is indeed correct.

Table 1 ^{1}H-NMR data of the pyrroloindolones 8a and 8b determined at 80 MHz in $CDCl_3$ (J in Hz)

	H-1	H-2	R-3	H-5	H-6	H-7	H-8		
8a*	6.78	6.31	7.07	7.11	7.42	7.13	7.58		
8b	6.69	5.98	2.51	7.17	7.39	7.11	7.58		
	$J_{1,2}$	$J_{1,R}$	$J_{2,R}$	$J_{5,6}$	$J_{5,7}$	$J_{5,8}$	$J_{6,7}$	$J_{6,8}$	$J_{7,8}$
8a*	3.7	0.8	2.6	7.8	0.8	0.7	7.7	1.3	7.4
8b	3.7	0.4	0.8	7.9	0.8	0.7	7.7	1.4	7.4

* Chemical shifts and coupling constants are identical with those described in the literature for compound 8a (10,14).

Table 2 ^{13}C-NMR spectrum of 8b determined at 100.6 MHz in $CDCl_3$ (J in Hz)

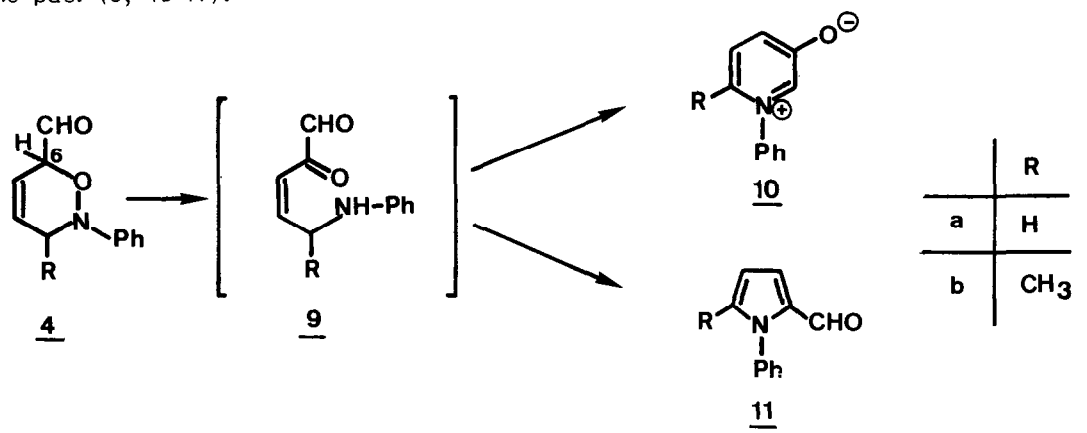
δ	^1J(C,H)	
178.05	-	C-9
142.99	-	C-4a
133.53	-	C-3
133.14	160	C-6
130.96	-	C-9a
130.14	-	C-8a
124.29	162	C-7
123.50	163	C-8
114.90	172	C-2
113.59	176	C-1
110.54	164	C-5
12.65	129	Me

Table 3 $^1J(^{13}C-^{13}C)$ coupling constants and $^{13}C-^{13}C$ isotope-effects upon the chemical shifts of 8b as determined at 100.6 MHz in $CDCl_3$ (J in Hz)

i,j	J(i,j)Hz	Δ(i)*Hz	Δ(j)*Hz
3,Me	49.5	-0.3	-0.9
3,2	65.9	-2.1	-2.4
2,1	53.3	-1.9	-1.7
1,9a	68.4	-1.7	-1.6
9a,9	71.4	-0.9	-0.3
9,8a	54.4	-0.4	-1.0
8a,8	63.8	-1.7	-1.4
8,7	55.7	-1.8	-1.8
7,6	58.0	-1.8	-1.8
6,5	57.1	-1.5	-1.8
5,4a	68.2	-1.8	-1.6
8a,4a	60.0	-1.7	-1.4

* Δ(i) and Δ(j) represent the isotope-effects upon the C_i and Cj carbon atoms respectively when the coupling C-atom under consideration is ^{13}C.

The formation of the two sets of reaction products 7/8 and 10/11 is essentially due to the acidity of hydrogen atom H-6 of the adducts 4. Base promoted deprotonation of H-6, followed by a ß-elimination leads to the acyclic intermediate 9. Intramolecular nucleophilic condensation of nitrogen with the aldehyde carbonyl (the more reactive partner), or with the ketone carbonyl (the less reactive partner) can lead to 10 and 11 respectively. On the other hand part of the adducts 4 can equilibrate with the conjugated enol tautomers 5, which can then undergo a hetero-Cope rearrangement, leading ultimately to pyrroloindole compounds 7, as indicated in the reaction scheme. Hetero-Cope rearrangements of N-phenyl-O-vinylhydroxylamine derivatives have already been described in the past (5, 15-17).



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