

ENAMINE CHEMISTRY—XI*

THE REACTION OF ENAMINES WITH STYRENE OXIDE†

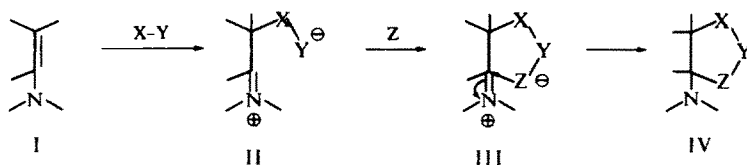
P. JAKOBSEN and S.-O. LAWESSON

Department of Organic Chemistry, University of Aarhus, 8000 Aarhus C, Denmark

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Abstract—Reaction of cyclic enamines with styrene oxide has been shown to give cyclic O,N-ketals having a furan nucleus. Dilute acidic hydrolysis of 2-phenyl-8-(N-pyrrolidino)perhydrobenzofuran, V, prepared from 1-pyrrolidino-1-cyclohexene, gave 2-(2-hydroxy-2-phenylethyl)cyclohexanone, VIII. Treatment of V with oxalic acid gave 2-phenyl-2,3,4,5,6,7-hexahydrobenzofuran, VI, which by acidic hydrolysis produced VIII, and by aromatization with sulphur was converted to 2-phenylbenzofuran. Mechanistic considerations for this new reaction are presented.

IN THE enamine field^{1,2} several new types of cycloaddition reactions have been found during recent years, leading to 4, 5 and 6-ring compounds. Except for the 4-ring compounds, which are isolated in rare cases only, and mostly are postulated as intermediates, the other ring compounds are found as stable species. Some of these ring compounds are formed according to the same general principle, namely that a zwitterion intermediate collapses leading to the cyclic product by a self-trapping mechanism. 5-Ring compounds, for instance, can be formed by two routes: the first one³⁻⁶ is the so-called 3-component reaction, meaning that an enamine, I, is reacted with two reagents, x-y and z, giving the final product, IV. As intermediates the two zwitterions II and III are postulated, of which the last one collapses under ring closure to give IV.



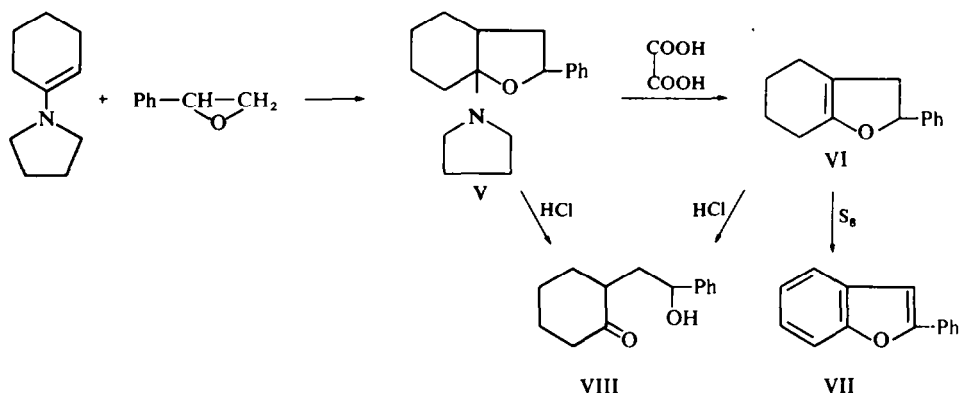
An intermediate zwitterion of type III can also be produced by the reaction of an enamine with a suitably chosen reagent like N-carbethoxyaziridine.⁷ We now wish to describe a new cyclization reaction in which a zwitterion, related to III, is involved.

It is well-known, that nucleophilic reagents attack oxiranes,⁸ whereby the ring is opened. It was thus anticipated that enamines, being nucleophilic reagents, also should cleave oxiranes. However, the anticipated reaction did not proceed at all at room or somewhat elevated temperature, as only starting material was recovered.

* Part X: J. Ø. Madsen and S.-O. Lawesson, *Tetrahedron*, **24**, 3369 (1968).

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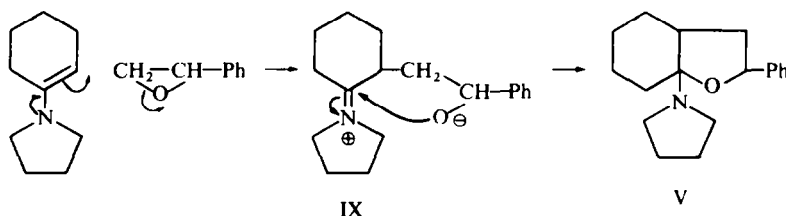
On the other hand, when the enamine and the oxirane were heated without solvent at about 230° the expected reaction did occur. Thus 1-pyrrolidino-1-cyclohexene and styrene oxide gave 2-phenyl-8-(N-pyrrolidino)perhydrobenzofuran, V, in 86% yields.



The ring structure of V was established by treatment of it with oxalic acid which removed pyrrolidine to give 2-phenyl-2,3,4,5,6,7-hexahydrobenzofuran, VI. Compound VI is smoothly aromatized with elemental sulphur to 2-phenylbenzofuran, VII. Compound V as well as VI, when hydrolyzed with hydrogen chloride solution, both produce 2-(2-hydroxy-2-phenylethyl)cyclohexanone, VIII.

All the new compounds (Table 1) had the correct elemental analysis and their NMR spectra were consistent with the assigned structures. The IR spectrum of VI showed a strong band at 1700 cm^{-1} ($\text{C}=\text{C}$ stretch in a vinyl ether); VII were in all respect (IR, NMR, m.p.) identical with authentic 2-phenylbenzofuran. In VIII strong IR bands at 3400 and 1690 cm^{-1} also proved the structure.

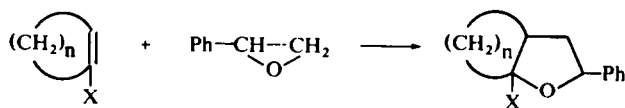
As to the mechanism, it is suggested that the first step is an attack of the enamine on the oxirane to give the zwitterion IX, which then collapses to give V as follows:



Attempts to extend this new reaction to related compounds showed that low-boiling epoxides, even in high-boiling solvents, did not react with enamines. We have therefore limited this investigation to the easily available styrene oxide but it is suggested that other epoxides with a suitable boiling point and structure also would react similarly. In Table 1 we have listed the produced cyclic O,N-ketals. Even if the reaction time was increased to 24 hr the enamines derived from the following carbonyl compounds did not react but only gave back the starting material: 2-isopropylcyclohexanone, n-butyraldehyde, isobutyraldehyde and acetophenone.

Reactions with enamines derived from β -dicarbonyl compounds only produced traces of high-boiling oils, which we have not tried to identify.

TABLE 1. PREPARATION OF O,N-KETALS ACCORDING TO THE FOLLOWING REACTION:



X	n	B.p. (mm Hg)	n_D^{25}	Yield %		Analyses (%)		
						C	H	N
Pyrrolidine	4	133 (0.13)	1.5473	86	Calc.	79.66	9.29	5.16
					Found	79.82	9.37	5.20
Morpholine	4	149 (0.1)	1.5455	38	Calc.	75.22	8.77	4.87
					Found	74.79	8.68	4.91
Piperidine	4	139 (0.15)	1.5438	60	Calc.	79.95	9.54	4.31
					Found	80.08	9.34	4.47
Pyrrolidine	3	119 (0.05)	1.5449	55	Calc.	79.33	9.01	5.44
					Found	78.93	9.13	5.60
Morpholine	3	148 (0.15)	1.5457	90	Calc.	74.69	8.48	5.12
					Found	74.10	8.33	5.39
Morpholine	5	142 (0.12)	1.5457	10	Calc.	75.72	9.03	4.65
					Found	75.16	8.94	5.01

EXPERIMENTAL

NMR spectra were recorded in CCl_4 at 60 Mc/s on a Varian A-60 spectrometer with TMS as internal reference standard (δ units). IR spectra were recorded on a Perkin-Elmer model 221 spectrophotometer. Analysis were made by Drs. F. B. Strauss and G. Weiler, Oxford, England, and Dr. A. Bernhardt, Mülheim (Ruhr), Germany. B.ps and m.ps are uncorrected.

As the procedure for the preparation of the cyclic O,N-ketals, is quite simple and general, only one example is given in detail.

2-Phenyl-8-(N-pyrrolidino)perhydrobenzofuran, V. 1-Pyrrolidino-1-cyclohexene (15.1 g; 0.1 mole) and styrene oxide (24 g; 0.2 mole) were heated with stirring for 4 hr (oil-bath-temp = 230°). After cooling, the reaction mixture was transferred to a distillation flask with a short Vigreux column and distilled at reduced press to give the title compound, b.p. 133° 0.13 mm Hg; $n_D^{25} = 1.5473$, yield: 23.3 g (86%). The NMR spectrum (in CCl_4) displayed 5 aromatic protons at 7.1–7.4 ppm, a quartet (1H, the proton in the 2-position) centred at 5 ppm, a triplet (4H, protons at the α -positions of pyrrolidine) at 2.9 ppm and a broad envelope (15H) at 1.4–2.5 ppm.

2-Phenyl-2,3,4,5,6,7-hexahydrobenzofuran, VI. Compound V (13.5 g; 0.05 mole) and oxalic acid (4.5 g; 0.05 mole) dissolved in 200 ml dioxan, were heated on a steam bath for 3 hr. After standing overnight the oxalate was filtered off. The soln was concentrated under vacuum, dissolved in ether, washed with water and dried (CaCl_2). Distillation gave VI as a colourless liquid, b.p. 76° 0.04 mm Hg; $n_D^{25} = 1.5499$, yield: 5.5 g (55%). (Found: C, 84.79; H, 8.50. Calc.: C, 84.90; H, 8.95%). In addition to the 5 aromatic protons at 7.2–7.3 ppm the NMR spectrum displayed a quartet (1H, proton at C-2) centred at 5.4 ppm and an envelope (10H) at 1.5–3.0 ppm.

2-Phenylbenzofuran, VII. Compound VI (5.0 g; 0.025 mole) and elemental sulphur (2.4 g; 0.075 mole) were heated for 4 hr on a sand-bath at 175°. The temp was then increased to 210 and kept there for 2 hr. Steam distillation of the reaction mixture, recrystallization from EtOH and subsequent sublimation gave 2.9 g (60%) of VII, m.p. and mixed m.p. 121°. (Found: C, 86.66; H, 5.10. Calc: C, 86.57; H, 5.19%). The IR and NMR spectra were identical with those of authentic 2-phenylbenzofuran.

2-(2-Hydroxy-2-phenylethyl)cyclohexanone, VIII. Compound V (8.1 g; 0.03 mole) was stirred with 50 ml 10% HCl at room temp. After 24 hr the title compound crystallized, m.p. 80° (90% petrol + 10% diethyl ether), yield: 3.9 g (60%). (Found: C, 77.18; H, 8.08. Calc: C, 77.03; H, 8.31%). The IR spectrum showed strong bands at 3400 (OH), 1690 (C=O), 1430, 1050, 1005, 950 and 935 cm^{-1} . The NMR spectrum showed 5 aromatic protons at 7.1–7.3 ppm, a quartet (1H) centred at 5.2 ppm, a singlet (1H, OH) at 3.1 ppm and a broad envelope (11 H) at 1.3–3.0 ppm.

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