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THE REACTION OF ENAMINES WITH EPOXIDES

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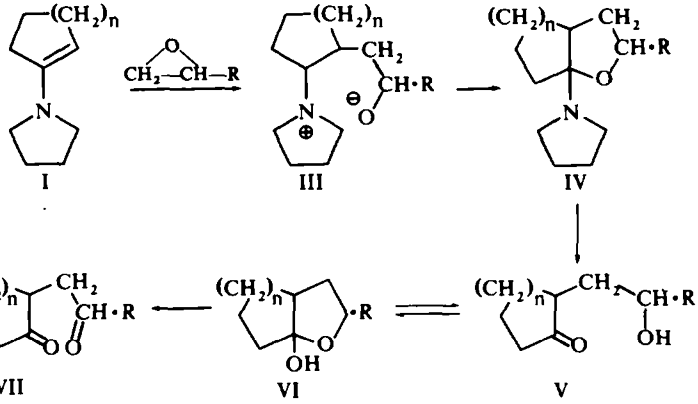
Abstract—Epoxides are found to undergo nucleophilic ring opening on reaction with enamines of cyclic ketones. The reaction provides a convenient route to 1,4-hydroxy-ketones.

With a view to finding a convenient route to 1,4-hydroxyketones required for Fischer indolization studies, the reaction of enamines with epoxides was investigated. It was expected (Scheme A) that the nucleophilic C atom of an enamine I, would cleave the ring of an epoxide II, to give via the zwitter ion III, an intermediate N,O-ketal IV which on hydrolysis would yield the required hydroxyketone V.

Scheme A



Initial experiments on the reaction between 1-pyrrolidino-1-cyclohexene and ethylene oxide in a number of solvents such as benzene, dioxan, acetonitrile and dimethylformamide, carried out between 0–5°, produced only traces of neutral material containing both OH and CO absorptions in its IR spectrum. Likewise, the reaction of propylene oxide in the same solvents, at their b.p., gave rise to only trace quantities of the required product. It therefore appeared that the expected reaction took place, albeit in low yields. Since it is stated that the alkylation of enamines with electrophilic olefins is enhanced by polar solvents and high temperatures,[1] it was decided to repeat the experiments with ethylene and propylene oxides and 1-pyrrolidino-1-cyclohexene in dimethylformamide at elevated temperatures. The reactions were carried out in sealed evacuated tubes over a range of temperatures between 90–170°. It was found that at 140° after 26 hr, the above enamine gave with ethylene oxide, after hydrolysis, a 33% yield of 2-(2-hydroxyethyl)cyclohexanone (Vb; Table 1). Propylene oxide under similar conditions gave a good yield of 2-(2-hydroxypropyl)cyclohexanone (Vc). Both ketones were identified by conversion into their known O-acetyl derivatives[2,3] and the 2,4-dinitrophenylhydrazones of the latter.

The total neutral product from the reaction of propylene oxide and 1-pyrrolidino-1-cyclohexene was found on analysis by VPC to be homogeneous, confirming that the ring opening of the epoxide took place (as in Scheme A) by attack on the least substituted epoxide C atom, as anticipated if the reaction was of the conventional S_N2 type believed to occur in the reactions of epoxides with bases.[4-6]

TABLE 1

V	N	R	%yield
a	1	Ph	42
b	2	H	33
c	2	Me	60
d	2	Ph	50
e	3	Ph	56

Whereas ethylene and propylene oxides required sealed tubes for reaction, it was found that styrene oxide reacted readily in refluxing dimethylformamide with the pyrrolidine enamines of cyclopentanone, cyclohexanone and cycloheptanone to give the ketones Va, Vd and Ve respectively. From these reactions was also isolated a basic product, 1-phenyl-2-(1-pyrrolidino)ethanol.[7] It was not established whether this arose from the direct N-alkylation of the enamines or from the reaction of the pyrrolidine produced on the hydrolysis of the intermediate IV with excess unreacted styrene oxide.

The structures of the products were confirmed by the oxidation of Vd into a diketone VII identical with α-(2-oxocyclohexyl)acetophenone which was also obtained from the reaction[8] of phenacyl bromide and 1-pyrrolidino-1-cyclohexene. It is interesting to note that although the ketones Va, Vc, Vd and Ve show a CO absorption peak of medium intensity in CCl_4 solution, this absorption is absent for Vc, Vd and Ve in the mulled state. In solution, therefore, an equilibrium exists between the open chain hydroxycarbonyl structure (V) and the cyclic hemiketal structure (VI).

The above work and structure of product is in agreement with the findings of Jackobsen and Lawesson.[9] They reported the reaction of styrene oxide with 1-pyrrolidino-1-cyclohexene, in the absence of solvents, and isolated the N,O-ketal IV (R = Ph). The ketal undergoes hydrolysis and dehydration on treatment with oxalic acid to give 2-phenyl-2,3,4,5,6,7-hexahydrobenzofuran, and the latter on acid hydrolysis gives Vd.

EXPERIMENTAL

The m.ps were determined on an Electrothermal apparatus and are uncorrected. The IR spectra were recorded on a Unicam S.P.200 spectrophotometer and the VPC was carried out on the Perkin–Elmer F 11 gas chromatograph. The reactants and solvents used were all laboratory grade reagents.

2-(2-*Hydroxyethyl*)*cyclohexanone* Vb.

(a) To a soln of 1-pyrrolidino-1-cyclohexene (0·1 mole) in DMF (100 ml) cooled to 0° was added ethylene oxide (0·21 mole). This soln was stoppered and kept for 24 hr in a refrigerated cabinet between 0–5°. The soln was then allowed to attain room temp and after addition of water (20 ml) was boiled under reflux for 30 min. The resultant mixture was diluted with water (100 ml) and extracted with ether (3 × 50 ml). The ethereal extracts were combined and washed with 2N HCl acid until all the basic material was removed and then washed with sat $NaHCO_{3aq}$ and dried. Evaporation of the ether under reduced press yielded a pale yellow oil (3·2 g) which exhibited in the IR a weak peak at 3500 cm^{-1} (OH) and a strong 1700 cm^{-1} (CO peak). Except for OH absorption, the spectrum was for all practical purposes superimposable on that of pure cyclohexanone. VPC on an apiezon column at 200° confirmed the presence of two components in the product, the major one being cyclohexanone.

The above experiment was carried out using different solvents with varying condition. Thus it was found that in benzene, acetonitrile, methylene chloride and dioxan for periods of 24–72 hr at temps of 4° or 18° there was no appreciable improvement in the yield of product.

(b) A cooled solution of 1-pyrrolidino-1-cyclohexene (0·5 mole) and ethylene oxide (1·10 mole) in DMF (100 ml) was placed in a thick walled glass vessel. The mixture was cooled in liquid N_2, the vessel was evacuated and sealed. After allowing the vessel and its contents to attain room temp, it was placed in an oven at 140° and kept at this temp for 26 hr. On cooling, the vessel was opened and the soln worked up, as in the previous experiments under (a) to yield a pale yellow oil (12·0 g; 33%) which on acetylation with AC_2O in pyridine gave a product identical in all respects with 2-(2-acetoxyethyl)cyclohexanone b.p. 124/8 mm (lit.[2] 142/15 mm) D.N.P. m.p. 109° [*lit*[2] 109–111°).

2-(2-*Hydroxypropyl*)*cyclohexanone* (Vc).

A soln of 1-pyrrolidino-1-cyclohexene (0·25 mole) and propylene oxide (0·5 mole) in DMF (100 ml) was reacted as above at 150° for 25 hr. Work up produced a pale yellow oil (29 g) which on distillation gave a colourless oil (24 g, 60%) b.p. 96–98°/7 mm identical with 2-(2-hydroxypropyl)cyclohexanone, D.N.P. m.p. 105–108°. (Found: C, 53·04; H, 6·02; $C_{15}H_{20}N_4O_5$ requires: C, 53·50; H, (5·95). O-acetyl derivative b.p. 120°/7 mm (lit.[3] 66–69°/0·3 mm). D.N.P. m.p. 165–167°. (Found: C, 53·92; H, 6·15; $C_{17}H_{22}N_4O_6$ requires: C, 54·00; H, 5·82). VPC of a sample of the initial product on an apiezon column at 200° showed the presence of only one component.

2-(2-*Hydroxy*-2-*phenylethyl*)*cyclohexanone* (Vd).

A soln of 1-pyrrolidino-1-cyclohexene (0·25 mole) and styrene oxide (0·50 mole) in DMF was boiled under reflux for 4 hr. After adding water (30 ml) the boiling was continued for a further 30 min. The soln was cooled, diluted with water (100 ml) and ether extracted (3 × 50 ml). The combined ethereal extracts were washed, with 2N HCl acid until all basic material was removed, and then with sat Na_2CO_3:aq and dried. Evaporation of the ether under reduced press gave a thick yellow oil which rapidly crystallized. The crude material (30 g) was briefly washed with cold light petroleum and recrystallized from the same solvent to give a colourless crystalline product (27 g 50%) of 2-(2-hydroxy-2-phenylethyl)cyclohexanone m.p. 84° (lit.[9] m.p. 80). The product shows the following absorption peaks in the IR (Nujol mull) 3250 cm^{-1} (s) (OH), 1010, 1070 cm^{-1} (s) ketal and in CCl_4 soln, 3550 cm^{-1} (m) (free OH) 3350 cm^{-1} (m) (H-bonded OH), 1700 cm^{-1}(m) (ketone CO) 1020, 1060 cm^{-1} (s) (ketal). The product failed to give a D.N.P. derivative.

1-*Phenyl*-2-(1-*pyrrolidino*)*ethanol*

The acid washings from the above reaction were made alkaline with 10% NaOH:aq and the resultant oil was ether extracted (3 × 50 ml). The combined rthereal extracts were dried and evaporated under reduced press on the steam bath to yield a pale yellow oil which solidified on standing. Crystallization from 60–80° pet ether gave 16·60 g of colourless material m.p. 57° (lit.[7] 57–58°).

Oxidation of 2-(2-*hydroxy*-2-*phenylethyl*)*cyclohexanone*

A solution of the ketone (1·1 g) in acetone was treated with CrO_3 in H_2SO_4 and left for 5 min. The resultant dark green soln was poured into excess water (50 ml) and ether extracted (3 × 10 ml). The combined ethereal extracts were washed with Na_2CO_3:aq dried and evaporated under reduced press to give a colourless oil (0·48 g) which crystallized on triturating with ether–light petroleum. The product was identical with an authentic sample of α-(2-oxocyclohexyl)acetophenone which was prepared by reacting phenacyl bromide with 1-pyrrolidino-1-cyclohexene.[8]

2-(2-*Hydroxy*-2-*phenylethyl*)*cyclopentanone*(Va)*and* 2-(2-*hydroxy*-2-*phenylethyl*)*cycloheptanone* were prepared in 42% and 56% yields respectively under the same conditions as the corresponding cyclohexanone (Vd).

Compound Va b.p. 176°/8 mm. (Found: C, 76·6; H 7·74. $C_{13}H_{16}O_2$ requires: C, 76·50; H, 7·83%). Absorption in the IR shows 3400 cm^{-1} (s) (OH), 1720 cm^{-1} (s) (ketone CO).

Compound Ve m.p. 107° (from pet ether). (Found C, 77·96; H, 8·2. $C_{15}H_{20}O_2$ requires: C, 77·5; H, 8·6%). Absorption in the IR (Nujol mull) shows 3330 cm^{-1}, (OH) several peaks 1000–1100 (s) (ketal) and in CCl_4 soln, 3550 cm^{-1} (free OH), 3330 cm^{-1} (H-bonded OH), 1700 cm^{-1} (ketone CO).

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