Reductive Cyclization of Disubstituted Pyridines and Intramolecular Aldolization of Unsymmetrical Diketones

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Summary The relative proportions of alternative cyclohexenones formed on the one hand from systems of the type 2-CH$_2$R,6-methylpyridine by reductive cleavage, and on the other hand from systems of the type Ac[CH$_2$]$_3$CO·CH$_2$R by alkaline cyclization may be different and may depend on the steric requirements of R.

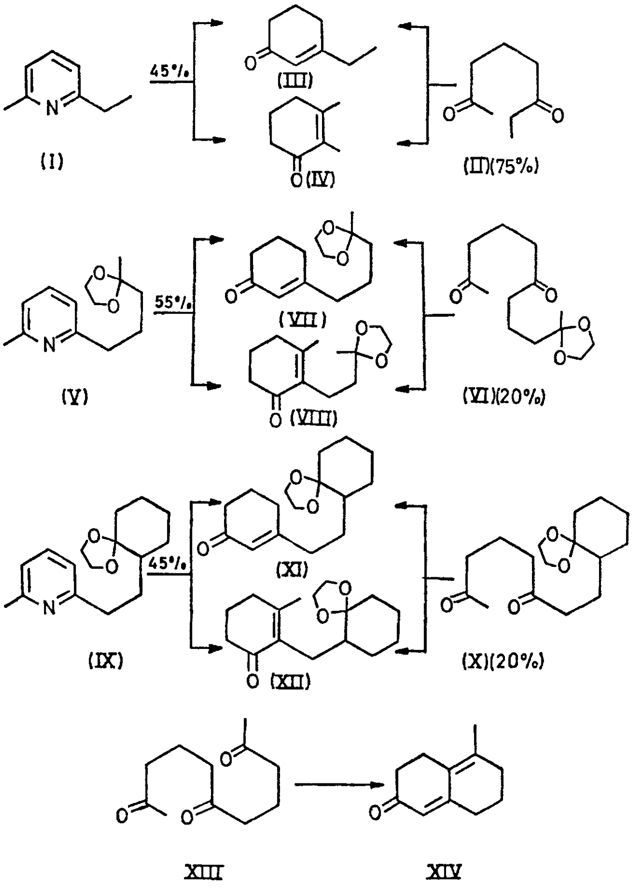
In the preceding communication, the question of the degree of intermediacy of diketones in the hydrolytic cyclization of dihydropyridines was unresolved,[1] and a steric branching effect was proposed to account for the cyclization of a 7-substituted heptane-2,6-dione to a 3-substituted, rather than to the precedented 2,3-disubstituted cyclohexenone.[2,3] We present here further relevant data.

We used pyridines (I), (V),† ‡ and (IX)[5] as substrates, and each pyridine was subjected to Birch reduction [Na–NH$_3$ (1·2 equiv.)–EtOH (1 equiv.)]. The resultant dihydro-systems were converted into the cyclohexenones shown, *via* two pathways: hydrolytic cyclization [NaOH–EtOH (3 equiv.); 3 h; room temp.], or cleavage§ to diketones (II),† (VI),† and (X).† In the case of (II), dihydro-(I) was treated with dilute acid. Compounds (VI) and (X) were obtained by brief exposure of dihydro-(V) and (IX) respectively, to aqueous alkali for 1 min.[1] Diketones (II), (VI), and (X)¶ were purified and subjected to base-induced aldolization [NaOH–aqueous EtOH (3 equiv.); 3 h; room temp.]. Each run was highly reproducible; the cyclohexenones were stable under the reaction conditions. The ratios of products obtained *via* the two routes are shown in the Scheme.

For (I) and (V), reduction by the hydrolytic cyclization route gave a different ratio of products from the internal aldolization route starting with the *bona fide* diketones. Control experiments showed that ammonia, produced during hydrolysis of the Birch reduction products, is not responsible for this disparity.

We thus conclude that, to a substantial extent, the dihydropyridine pathway involves an intermediate other than the diketone, and possibly involves partial hydrolysis to an intermediate imine or enamine, which produces, upon cyclization, more of the 3-substituted isomer [(III) and (VII)] than is obtained from the diketone route.

Whatever the nature of the process, it becomes less detectable as the diketone cyclization itself favours the trisubstituted isomer. This is apparently the case with the ratio of (XI) to (XII) derived from (IX) and (X). The drastic change in the course of cyclodehydration of (II), (VI), and (X) may be ascribed to a branching effect [(II) *vs.* (VI)] which increases in importance with its proximity to the nearest ring centre.



Scheme. *Ratios of yields of products are as follows:* (III):(IV) = 1:3·5 *from* (I), 1:20 *from* (II); (VII):(VIII) = 1:1·5 *from* (V), 1:3·5 *from* (VI); (XI):(XII) = 1:4·5 *from* (IX) *and from* (X).

Finally, Birch reduction of (V) followed by cleavage with 10% aqueous H$_2$SO$_4$ gave the crystalline undecane-2,6,10-

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† Prepared in 70% yield by the alkylation of the monolithio-salt of 2,6-lutidine, (*via* n-butyl-lithium + α-picoline in hexane) with 1-bromo-3-ethylenedioxybutane.[4]

‡ The structures of all new compounds are consistent with their i.r., n.m.r., and mass spectra. Enones were further characterized by their u.v. spectra.

§ Yields for the conversion by the Birch reduction–hydrolytic cyclization are shown.

¶ Yields of the diketones are given. As before[1] it should be emphasized that the isolation of (VI) and (X) in considerably lower yield than those of the ultimate enone products does not indicate their sole intermediacy. While the yield of (II) was quite high it was, however, obtained by acidic hydrolysis. The conversion of the diketones into the cyclohexenone mixtures was essentially quantitative.

trione (XIII),† m.p. 88—89°. Treatment of the latter with toluene-*p*-sulphonic acid in acetic acid (75—80°; 16 h) gave the known[6] (XIV) (70%).

These studies were conducted under Public Health Service grants. Mass spectra were measured by Mr. Richard Montgomery.

(*Received*, 30*th December* 1971; *Com.* 2208.)

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