Tetrahedron. Vol. 24, pp 4083 to 4089 Pergamon Press 1968. Printed in Great Britain

CYCLODEHYDRATION OF KETO PYRIDINES–TOSYL ACID CLEAVAGE OF 2-PYRIDYL ETHYL ETHERS*

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(*Received in USA 5 September* 1967; *accepted for publication 27 November* 1967)

Abstract—The cyclodehydration of 2-2-(2-ethoxy-6-pyridyl)ethyl cyclohexanone (II) under the influence of *p*-toluenesulfonic acid, has been demonstrated. Attending this reaction is a de-ethylation process leading to the formation of the tricyclic pyridone, III, as well as the tricyclic pyridyl ether, V, and ethyl-*p*-toluenesulfonate. A five-step synthesis of II, starting with 6-methyl-2-pyridone (VIII) is described.

THE resistance of the pyridine ring to electrophilic attack[1] is a well known phenomenon which serves as a restraining influence on synthetic planning in this system. In an effort to better circumscribe the operational limits of this resistance, we studied compounds I and II with respect to a projected cyclodehydration reaction. These compounds offered the possibility of examining the effects of intramolecularity on this resistance. Compound II allowed for the opportunity to observe, at least to a qualitative extent, the effect of a sharp increase in the nucleophilic capability of the pyridine ring on the reaction. Collaterally, if such a transformation were successful, it would be of some utility in the construction of fused heterocyclic systems of relevance to the synthesis of azasteroids.

After a wide variety of treatments under acidic conditions, ranging in strength from pyridine hydrochloride to sulfuric acid, compound I[2] was recovered in high yield. No evidence for the occurrence of cyclodehydration was suggested by these experiments. Apparently, the intramolecular nature of the process is inadequate to overcome the difficulty of generating a positive charge on the pyridine ring. In the case of the strongly acidic catalysts, the problem is undoubtedly compounded by protonation (or co-ordination) of the pyridine nitrogen which renders the ring particularly resistant to further electrophilic encroachment. As the acid strength is weakened, the concentration of protonated carbonyl (oxonium) species is correspondingly lowered, thereby diminishing the concentration of active electrophile.

However, compound II did exhibit reactivity in the desired sense. Thus after heating it with excess *p*-toluenesulfonic acid (tosyl acid) in toluene solution at 140–142°, three products were isolated (see Experimental for details of workup and purification).

A crystalline compound, m.p. 248–249°, is assigned structure III (42% yield) on the basis of its combustion analysis and spectral properties. The maxima at 6·00 and 6·05 μ in its IR spectrum are consistent with the presence of a vinyl pyridone system.

* These studies were supported by a grant from the Damon Runyan Memorial Foundation.

† This work comprises a section of the thesis submitted by Martin L. Feldman to the Division of Natural Sciences, University of Pittsburgh, in partial fulfillment of the Ph.D. degree.

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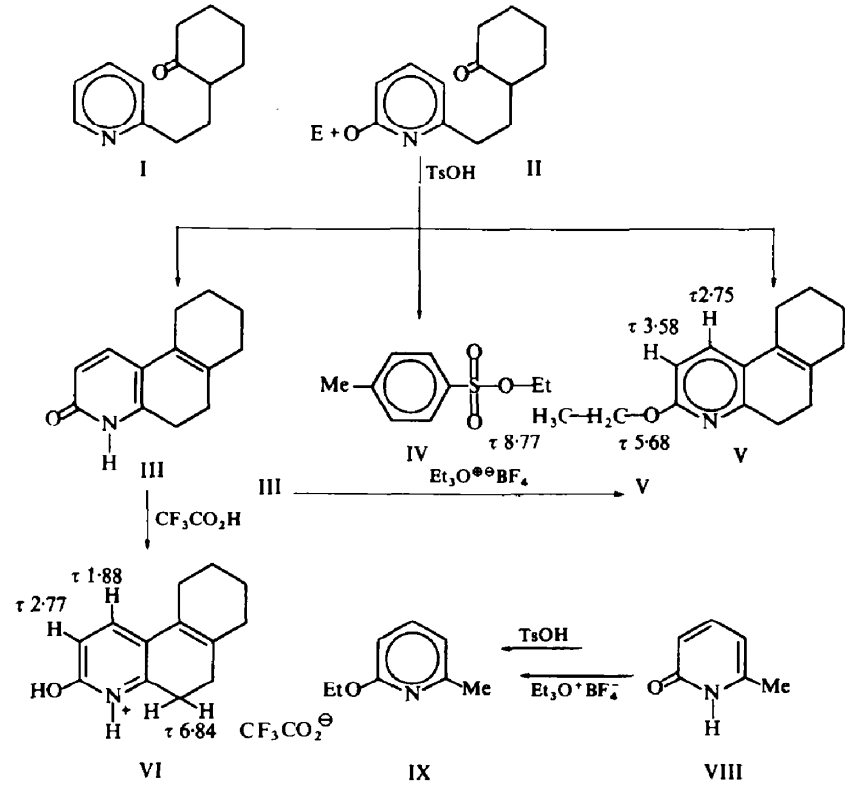
Its NMR spectrum, measured in trifluoroacetic acid, where the transformation III → VI would occur, exhibits signals,* areas and couplings as follow: $\tau = 1{\cdot}88$ (1H, doublet, $J = 10$ c/s); 2·77 (1H, doublet, $J = 10$ c/s); 6·84 (2H, triplet, $J = 7$ c/s); 7·30–8·32 (10H, unresolved multiplet). The assignments are shown in structure VI.

One of the liquid products (20% yield) was readily identified as ethyl *p*-toluenesulfonate (ethyl tosylate, IV) by comparison of its IR spectrum and gas chromatographic properties with those of an authentic sample.

Structure V is assigned to the oily minor product (8% yield) on the basis of its combustion analysis and spectral properties. Its IR spectrum ($\lambda_{max}^{CH_2Cl_2}$ 6·05, 6·30, 6·39 μ) is consistent with the vinyl pyridine formulation. Its NMR spectrum exhibits signals, areas and couplings as follow: τ_{CCl_4} 2·75 (1H, doublet, $J = 8$ c/s); 3·58 (1H, doublet, $J = 8$ c/s); 5·68 (2H, quartet, $J = 8$ c/s); 7·00–8·90 (15H, multiplet containing a triplet, $J = 7$ c/s, centered at 8·77 ppm). The assignments are shown in structure V.

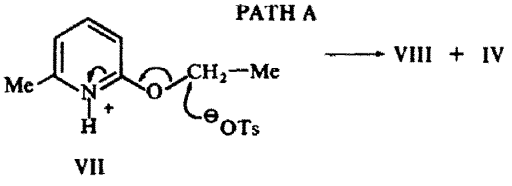
The structural relationship between the pyridone, III, and the pyridyl ether, V, was established by conversion of the former into the latter with triethyloxonium fluoborate.[3]

These results are summarized below:



* All NMR data are reported on the scale with an internal TMS reference at 10 ppm. The absence of signals for the "NH" or "OH" protons in structure VI is in accord with the observations of Griffin and Byrne during their studies of the NMR spectra of quinolones in trifluoroacetic acid. Unpublished results of C. E. Griffin and W. E. Byrne, University of Pittsburgh.

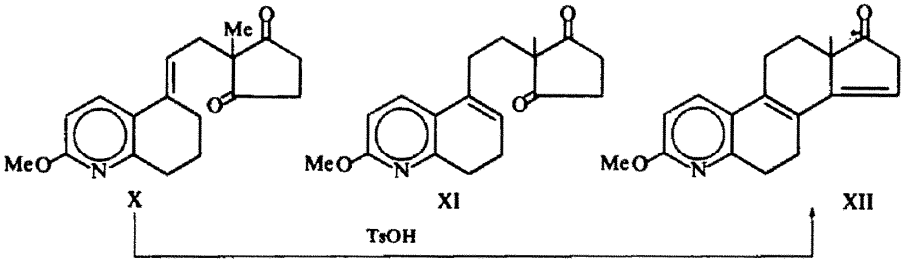
The conversion of an ethyl-α-pyridyl ether to a 2-pyridone and ethyl tosylate by heating the ether with tosyl acid was demonstrated in a simple case utilizing compound IX. Whether the ethyl tosylate (IV) is produced by a rather unusual nucleophilic attack of tosylate ion on the 2-ethoxypyridinium ion VII,[4] (path A) on whether it arises from tosylation of the ethyl alcohol which is in turn formed by a nucleophilic attack of water (present as water of hydration) on the same ion (path B), or from both of these routes is not clear. Regardless of this uncertainty, this method may be the one of choice for effecting this type of transformation.



The available data also do not allow for the delineation of the route which leads to the major product. Thus III might arise from a de-ethylated product, which then undergoes cyclodehydration in a manner well known for pyridones.[5,6] Alternatively it might arise from prior cyclodehydration to form V and subsequent de-ethylation.

Regardless of this unresolved question, there seems little doubt that compound V itself arises from a cyclodehydration of II, thus demonstrating the feasibility of intramolecular electrophilic attack on a suitably activated pyridine ring under relatively[1] mild conditions. In addition to its ability to stabilize the intermediate arising from attack of the oxonium ion on the pyridine ring, an ancillary effect of the ethoxyl function might be its base-weakening character.[7] This would tend to increase the concentration of the free pyridine relative to the presumably unreactive pyridinium ion.

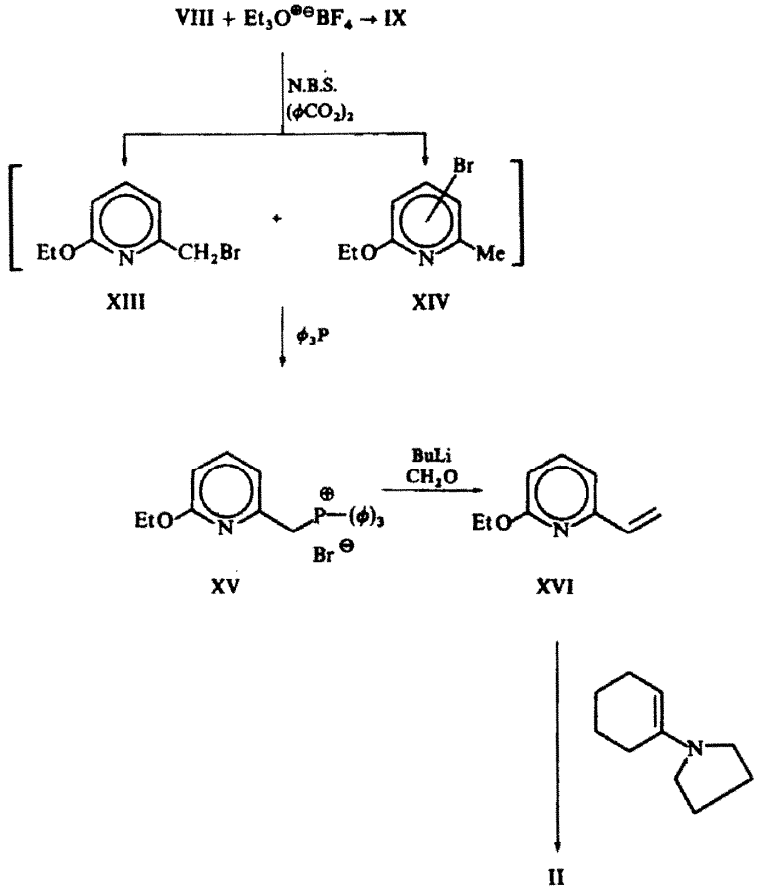
During these studies, there appeared a report of the conversion, X → XII, presumably *via* intermediate XI. Clearly, this case bears a vinylogous relationship to the one at hand. Although no yield of XII is specified, no mention is made of any pyridone formation. However, the conditions employed in the 4-azaestrone synthesis[8] differed somewhat from those employed in this study and this might account for the difference in results, if indeed, such a difference exists.



The synthesis of compound II started with 6-methyl-2-pyridone (VIII). The pyridone was converted to the pyridyl ether, IX, with triethyloxonium fluorborate.[6] Treatment of IX with N-bromosuccinimide in carbon tetrachloride in the presence of a one-tenth equivalent of dibenzoyl peroxide, afforded a mixture of ring and side chain halogenated products, XIII and XIV.[9] Spectral (NMR) analysis of the mixture indicated that it is composed of an approximately 1:1·5 ratio of these compounds. Treatment of this mixture with triphenylphosphine afforded a crystalline phosphonium salt which was assigned structure XV on the basis of its combustion analysis and spectral properties. The vinyl compound, XVI, was prepared from XV by a Wittig reaction with paraformaldehyde.

It was a source of some disappointment to find that the condensation of XVI with the pyrrolidine enamine of cyclohexanone under a variety of conditions produced, after hydrolysis, the desired compound, II, in a maximum yield of only 26%. This stands in contrast to the 71% yield of I obtained from the condensation of the same enamine with 2-vinyl pyridine. Unlike the latter case, extensive polymerization of the vinyl pyridine system was encountered with compound XVI.

The synthetic sequence is shown below.



EXPERIMENTAL

IR spectra were measured on a Beckman IR-8 spectrophotometer. NMR spectra* were obtained on a Varian A-60 instrument. M.ps and b.ps are uncorrected. Combustion analyses were conducted by the Galbraith Microanalytical Laboratories, Nashville, Tenn.

The ethylation of the pyridone, VIII

Preparation of IX. To a soln of 36·0 g (0·20 moles) triethyloxonium fluoborate[10] in 200 ml CH_2Cl_2, was added 15·6 g (0·14 moles) of VIII (Aldrich). The resultant soln was stirred at room temp for 1 hr, extracted with 100 ml 10% NaOH aq and dried over Na_2SO_4. Distillation at 18 mm afforded 14·0 g of VIII (71%) in a center cut b.p. 64–65° (lit.[11] 59–60°/18 mm). $\lambda_{max}^{CHCl_3}$ 6·26, 6·33 μ. τ_{neat} 2·70 (1H, tr, J = 8 c/s); 3·45 (1H, d, J = 8 c/s); 3·50 (1H, J = 8 c/s); 5·62 (2H, qu, J = 7 c/s); 7·63 (3H, s); 8·70 (3H, tr, J = 7 c/s).†

The cleavage of IX

Formation of IV *and* VIII. A soln of 4·9 g (0·035 moles) of IX and 13·3 g (0·07 moles) *p*-toluenesulfonic acid monohydrate (Fisher) in 20 ml toluene was heated at 140–145° for 24 hr. The soln was extracted with dil KOH aq, the aqueous portions being very slightly basic. The organic layer was concentrated and the residue was extracted with $CHCl_3$. The $CHCl_3$ soln was dried over Na_2SO_4 and the solvent was removed at the water pump leaving a residue which crystallized in part. Washing with ether gave 3·90 g (99%) of VIII. Evaporation of the ether left an oily residue which was shown to be IV by comparison of its IR spectrum and gas chromatographic behavior with those obtained from the authentic compound.

Bromination of IX

Formation of XIII *and* XIV. To a soln of 16·2 g (0·118 moles) of IX, in 150 ml CCl_4 was added 23·14 g (0·130 moles) N-bromosuccinimide and 0·5 g (0·002 moles) dibenzoylperoxide. The resultant mixture was stirred and heated under reflux for 1·5 hr. The color of the reaction mixture proceeded from white to deep orange to light yellow.

After cooling, the white solid (succinimide) was filtered. The solvent was removed at the water pump and the residue was distilled at 0·08–0·24 mm, giving 17·3 g‡ of a green, cloudy liquid from 56–75°; $\lambda_{max}^{CHCl_3}$ 6·34 μ.

Preparation of the phosphonium salt, XV

A soln of 17·2 g of the mixed bromo cpds (0·08 moles) and 21 g (0·08 moles) triphenylphosphine in 50 ml benzene was heated under reflux for 1 hr. Upon cooling, 21·5 g (39%)§ of a white solid, m.p. 220–221°, was obtained by filtration. (Found: C, 65·14; H, 5·78; N, 3·04. Calc. for $C_{26}H_{25}BrNOP$: C, 65·27; H, 5·73; N, 2·95%); $\tau_{CF_3CO_2H}$ 1·77 (18H, mu); 4·68 (2H, tr, J = 15 c/s); 5·44 (2H qu, J = 7 c/s); 8·50 (3H, tr, J = 7 c/s).

Preparation of XVI

In a flame dried, 3-neck round bottom flask equipped with a magnetic stirrer, reflux condenser and N_2 inlet was placed 9·56 g (0·02 moles) of XV, in 150 ml anhyd ether. To this was added 13 ml 15% n-BuLi in hexane (Foote). The reaction mixture immediately turned bright orange and gas was evolved. After evolution had stopped 1·3 g (0·04 moles) of vacuum dried paraformaldehyde was added and the mixture stirred for 3·5 hr at room temp. The reaction was quenched with 100 ml water, the organic layer was dried over Na_2SO_4 and the solvent was removed at the water pump at room temp. The residue crystallized in

* See footnote,* page 4084.

† d = doublet; qu = quartet; s = singlet; tr = triplet, etc.

‡ Attempts at a physical separation of the components of this mixture proved unrewarding. The ratio of the side chain substituted compound, XIII, to the sum of nuclear brominated compound(s) was ascertained by integrating the signal at τ 7·5 which is assigned to the side chain methyl group of the nuclear brominated compound relative to (a) the triplet (J = 7 c/s) centered at τ 8·75 which arises from the Me group of ether (common to both systems) and (b) a singlet, τ 5·65, which is assigned to the CH_2 protons of the bromomethyl side chain. Integration of either (a) or (b) relative to the signal of τ 7·5 leads to a ratio of XIII:XIV ≅ 1:1·15.

§ This is the yield of the conversion IX → XV.

part. The liquid was separated with a pipette and the solid was washed with cold ether. The washings were combined with the mother liquor, the solvent evaporated at reduced press and the residue was distilled over 0·20 g hydroquinine at 21 mm. There was obtained 1·85 g (62%) of XVI as a free-flowing liquid from 89–93°; $\lambda_{max}^{CHCl_3}$ 6·12, 6·34 μ. τ_{neat} 2·72 (1H tr, J = 8 c/s); 3·03–3·98 (4H, mu); 4·72 (1H, d of doublets, J_1 = 10 c/s, J_2 = 2 c/s); 5·65 (2H, tr, J = 7 c/s); 8·72 (3H, tr, J = 7 c/s). (Found: C, 72·53; H, 7·51; N, 9·22. Calc. for $C_9H_{11}NO$: C, 72·46; H, 7·43; N, 9·39%).

Preparation of II

A soln of 7·5 g (0·051 moles) of XVI and 8·0 g (0·053 moles) of the pyrrolidine enamine of XVII in 25 ml diglyme (distilled from CaH_2) was heated for 17 hr at 175–185° in pressure bottle. After cooling, the reaction mixture was poured into 200 ml water and stirred for 3 hr at room temp. The aqueous mixture was extracted with 300 ml ether. The ethereal soln was dried over Na_2SO_4, and the solvent was removed at the water pump. The residue was distilled at 0·2 mm affording 3·26 g of a distillate from 100–180° (26% crude yield). This material was purified by preparative GLC on a 5 ft 20% S.E.30 on chromosorb W column (He flow rate 86 ml/min) at 240° giving a retention time at 5·7 min; $\lambda_{max}^{CHCl_3}$ 5·83, 6·26, 6·34 μ. τ_{CCl_4} 2·67 (1H, tr, J = 8 c/s); 3·50 (2H, d, J = 8 c/s); 5·70 (2H, tr, J = 7 c/s); 7·18–8·93 (16H, m containing a tr, J = 7 c/s at 8·76 ppm).

The reaction of II *with* p-*toluenesulfonic acid formation of* III, IV *and* V

To a soln of 358 mg (1·5 mmoles) of II, in 5 ml dry toluene, was added 1·14 g *p*-toluenesulfonic acid. The mixture was heated at 140–142° for 17 hr in a borosilicate pressure bottle. After cooling, the mixture was made slightly basic with KOHaq and extracted with 150 ml CH_2Cl_2. The extract was dried over Na_2SO_4. Upon removal of the solvent, the residue crystallized in part. After washing with ether, 138 mg (42%) of compound III was obtained. One recrystallization from $CHCl_3$ afforded an analytical sample m.p. 248–249°. (Found: C, 77·23; H, 7·33. Calc. for $C_{13}H_{15}NO$: C, 77·58; H, 7·51%). See discussion section for spectral properties of III.

Evaporation of the ether soln left a residue which was purified through preparative gas chromatography (5 ft 20% S.E.30 chromosorb W column at 240° column temp and 56 ml/min flow rate), affording IV and V as oils at retention times of 2·0 and 6·3 min, respectively. The IR spectrum of IV was superimposable with that of authentic ethyltosylate and the retention time was identical.

Collection of the peak of 6·3 min retention time gave an 8% yield of V. (Found: C, 78·46; H, 8·50. Calc. for $C_{15}H_{19}NO$: C, 78·56; H, 8·35%). See discussion section for spectral properties of V.

The reaction of III *with triethyloxonium fluoborate*

Formation of compound VI. To a soln of 85 mg (0·39 mmoles) of III in 50 ml CH_2Cl_2 was added 84 mg (0·42 mmoles) triethyloxonium fluoborate. The soln was stirred for 1 hr and then extracted with dil NaOHaq. After drying over Na_2SO_4, the organic layer was stripped of solvent at the water pump. The IR spectrum and gas chromatogram of the residue (92 mg) indicated it to be essentially pure V, contaminated with traces of starting material, III. Preparative gas chromatography of this material (5 ft 20% S.E.30 on chromosorb W column, at a column temp of 240° and a flow rate of 6·2 ml/min) afforded 18 mg of V. The IR and NMR spectra of the material thus obtained were superimposable with those of V obtained from the previous experiment.

[1] cf. R. A. Abramovitch and J. G. Scala, *Advances in Heterocyclic Chemistry* Vol. 6; pp. 229–333. Academic Press, New York, N.Y. (1966).

[2] G. Singerman and S. Danishefsky, *Tetrahedron Letters* No. 33, 2249 (1964).

[3] cf. H. Meerwein, W. Florian, N. Schön and G. Stopp, *Liebigs Ann.* **641**, 1 (1961).

[4] For a very recent report suggesting the strong alkylating capabilities of alkoxypyridinium ions see: A. I. Meyers, A. H. Reine and R. Gault, *Tetrahedron Letters* 40, 4049 (1967).

[5] For an example of intermolecular attack on pyridones, see: R. Adams, J. Hine and J. Campbell, *J. Am. Chem. Soc.* **71**, 387 (1949). For an elegant cyclodehydration reaction on a pyridone see: R. N. Seeyle and D. W. Stanton, *Tetrahedron Letters* No. 23, 2633 (1966).

[6] For an instance of cyclodehydration in an aminopyridine (or iminopyridone) system, see: G. R. Lappen, *J. Am. Chem. Soc.* **70**, 3348 (1948); C. R. Hauser and M. J. Weiss, *J. Org. Chem.* **14**, 453 (1949).

[7] A. Albert and N. J. Phillips, *J. Chem. Soc.* 1794 (1956).
[8] M. A. T. Sluyter, U. K. Pandit, W. W. Speckamp and H. O. Huisman, *Tetrahedron Letters* No. 1, 87 (1966).
[9] For a study of the reaction of N-bromosuccinimide with various aromatic side chains, see: B. U. U.-Hoi, *Liebigs Ann.* **556**, 1 (1944). For a critical discussion of the subject, see: C. Djerassi, *Chem. Rev.* **43**, 271 (1948).
[10] H. Meerwein, E. Battenberg, H. Gold, E. Pfeil and G. Willfang, *J. Prakt. Chem.* **154**, 83 (1939).
[11] K. G. Cunningham, G. T. Neubold, F. S. Spring and J. Start, *J. Chem. Soc.* 2091 (1949).