

Notes

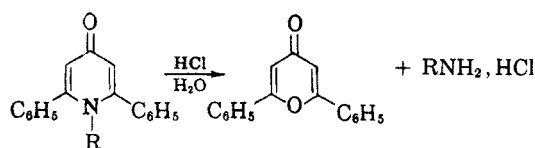
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Hydrolysis of 4-Pyridones

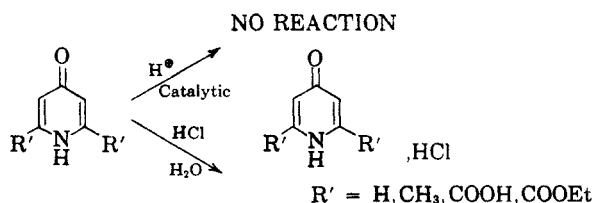
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Received March 25, 1957

During the course of studies on 2,6-diphenyl-4-pyridones as potential antimalarials¹ attempts were made to prepare the hydrochlorides of these compounds. It was found that these pyridones do not yield the desired hydrochlorides in aqueous medium but are converted back to 2,6-diphenyl-4-pyrone and the amine hydrochlorides. It was subsequently observed that this hydrolysis could be achieved by traces of mineral acid. It was also found that 2,6-diphenyl-4-pyridone hydrochloride is hydrolyzed to the pyrone in presence of water.

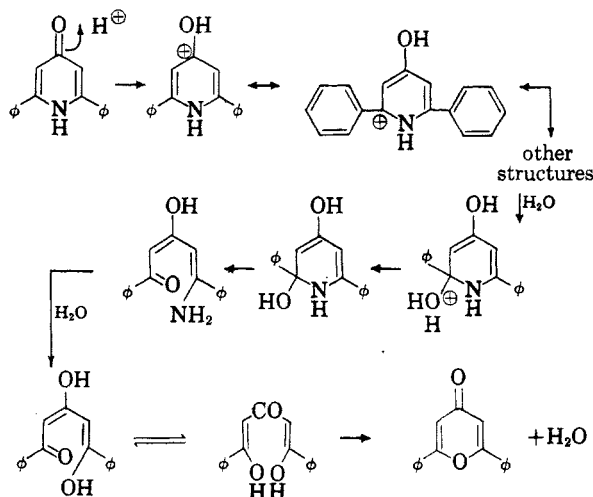


To find if this unusual hydrolysis was due to the presence of the phenyl substituents at the alpha positions a study using pyridones with the substituents H, CH₃, COOH, and COOEt was made. It was noticed that only 2,6-diphenyl-4-pyridones give the corresponding pyrone in the presence of catalytic amounts of acid. The other pyridones are unaffected by the presence of small amounts of mineral acid.



Examination of the Fischer-Hershfelder molecular models of these compounds indicated no particular strain induced by the two phenyl groups. The acid catalyzed hydrolysis probably proceeds by the following mechanism.

If the pyridone is considered as a vinylog of an acid amide the addition of a proton to the acyl oxygen results in the formation of a carbonium ion. Addition of a molecule of water follows and subsequent rearrangement results in the formation of the pyrone. The phenyl groups stabilize the carbonium ion due to resonance and indirectly even might fa-



ilitate the formation of the carbonium ion. This effect is absent in the case of pyridones where the alpha substituents are not phenyl groups.

EXPERIMENTAL

2,6-diphenyl-4-pyridone. To 5 g. of 2,6-diphenyl-4-pyrone was added 50 ml. of alcoholic ammonia. The whole was evaporated to dryness and the process repeated. The residue was crystallized from benzene to give the product; m.p., 178°; yield, 4.8 g. (m.p. reported,² 178°). The hydrochloride was prepared by passing dry HCl gas through a solution of the pyridone in benzene; m.p., 248–249° (m.p. reported,² 249°).

Hydrolysis of 2,6-diphenyl-4-pyridone. Two grams of the pure pyridone was dissolved in 20 ml. of water; to the aqueous solution was added two drops of concentrated hydrochloric acid. The white crystalline precipitate thrown out was collected, washed with water, and dried as product A. Yield, 1.9 g; m.p. 137°; recrystallized from water gives m.p. 138° (m.p., reported,³ for 2,6-diphenyl-4-pyrone, is 138°). A small quantity of the product A on evaporation to dryness with alcoholic ammonia leaves a residue, m.p. 178°, which gives with HCl gas in benzene a hydrochloride, m.p. 248–249°.

Hence product A was identified as 2,6-diphenyl-4-pyrone. Mixed melting point with an authentic sample showed no depression.

N-(p-chlorophenylbiguanyl)-2,6-diphenyl-4-pyridone. Five grams of 2,6-diphenyl-4-pyrone and 4.2 g. of p-chlorophenylbiguanide were refluxed in 30 ml. of alcohol for 8 hr. The product which separated on cooling was collected and crystallized from alcohol, m.p. 154°; yield, 6 g.

Anal. Calcd. for C₂₅H₂₀N₃ClO: N, 15.84. Found: N, 16.02.

Hydrolysis. Three grams of this pyridone was treated with 15 ml. of dilute hydrochloric acid (1:1). After standing for 15 min. the solid was collected, washed with water, and recrystallized from hot water, m.p. 137–138°. (This product was identified as 2,6-diphenyl-4-pyrone.)

The aqueous solution on basifying with sodium hydroxide gave a solid which after crystallization from alcohol gave

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m.p. 139° (reported⁴ m.p. for *p*-chlorophenyl biguanide 139–140°, mixed melting point showed no depression).

Action of dilute HCl on diethyl chelidamate. Four-grams of the pyridone was suspended in 20 ml. of water and treated with 0.5 ml. of concentrated HCl; after standing for an hour the solid was collected and washed with water; m.p., 80–81°; yield, 3.8 g. (Reported⁵ m.p. for diethyl chelidamate, 81°.) The product shows no depression in melting point when mixed with an authentic sample. Hence the pyridone was not hydrolyzed to the corresponding pyrone.

Action of dilute HCl on chelidamic acid. The chelidamic acid was treated with HCl using the same conditions as in the previous experiment. The product was identified as unchanged chelidamic acid.

Action of dilute HCl on 2,6-dimethyl-4-pyridone. Five grams of the pyridone was dissolved in 30 ml. of water and treated with three drops of concentrated HCl. On evaporation of the water a residue was obtained which was crystallized from water with m.p., 224–225°. This substance also gave a hydrochloride salt, m.p. 246–247°. (Reported⁶ m.p. for the pyridone is 225° and for the HCl salt 247°.) It may be concluded that no hydrolysis took place.

Action of dilute HCl on 4-pyridone. Using the same procedure as the previous one, 4-pyridone and HCl gave only unchanged pyridone as the product. The product gave a hydrochloride, m.p. 138–139°. (Reported⁷ m.p. 139°.)

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Synthesis and Rate of Acetolysis of 1-Bicyclo-[2.2.1]heptylmethyl Tosylate

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Received September 16, 1957

The mechanism and driving force of the Wagner-Meerwein rearrangement has been investigated by Winstein *et al.*¹ and it has been concluded that the acetolysis of neopentyl type halides proceeds with minimal solvent participation and neighboring group effects. Furthermore, the relief of steric strain *via* formation of an intermediate carbonium ion appears to have no accelerating effect on the reaction.

Acetolysis of 1-bicycloheptylmethyl² tosylate also may involve a minimum amount of solvent participation, and formation of an intermediate carbonium ion should not have any different steric effect on the rate than in the case of neopentyl tosylate. Should the migrating group not participate in the rate determining step of the rearrangement, it would be expected that the rates of acetolysis of

neopentyl tosylate and bicycloheptylmethyl tosylate would be nearly the same. However, should the migrating group participate in the rate controlling step, essentially through a nucleophilic displacement, it might be predicted that the acetolysis of bicycloheptylmethyl tosylate would be faster than that of neopentyl tosylate, for participation by the former would involve rearrangement to a bicyclo [2.2.2]octyl radical, with relief of some steric strain, and concomitant increase in driving force.

The preparation of 1-bicycloheptylmethyl derivatives has not been reported. However, methods have been described which lead to their synthesis, *via* bridgehead substituted bicycloheptanes. Many attempts to prepare bridgehead substituted bicycloheptanes have failed. Thus, *trans*-halogenation of bicycloheptane with *t*-butyl chloride and aluminum chloride gave only *exo*-2-chloro-bicycloheptane,³ and the peroxide-directed chlorination of bicycloheptane gave the same product.⁴ On the other hand, vapor phase nitration of bicycloheptane gave 1-nitrobicycloheptane,⁵ and 1-chlorobicycloheptane has been reported,⁶ although its method of preparation and physical properties were not described.

The Wagner-Meerwein rearrangement of 2-chlorobicycloheptane gives only the mirror image of the starting material, but rearrangement of 2,2-dichlorobicycloheptane should give 1,2-dichlorobicycloheptane. This reaction has been carried out in the camphane series by Houben and Pfankuch.⁷ The 2-chloro substituent can be selectively removed either by catalytic hydrogenation in the presence of base,⁸ or by means of a *trans*-halogenation reaction.⁹ The dichloride can be obtained from 2-ketobicycloheptane using phosphorus pentachloride.¹⁰ The ketone can be prepared by the method of Alder and Rickert.¹¹ Thus, 1-chlorobicycloheptane synthesized *via* the ketone, 2,2-dichloride and 1,2-dichloride, was converted to 1-carboxy-bicycloheptane *via* the lithium salt of bicycloheptane, the acid reduced to 1-hydroxymethylbicycloheptane, and the latter converted to its tosyl derivative.

The rate of acetolysis of the tosylate was determined in anhydrous acetic acid at 99.7°, using the method described by Winstein, Grunwald and

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