SYNTHESIS OF 3-HYDROXY-2-ALKYLPYRIDINES[1]

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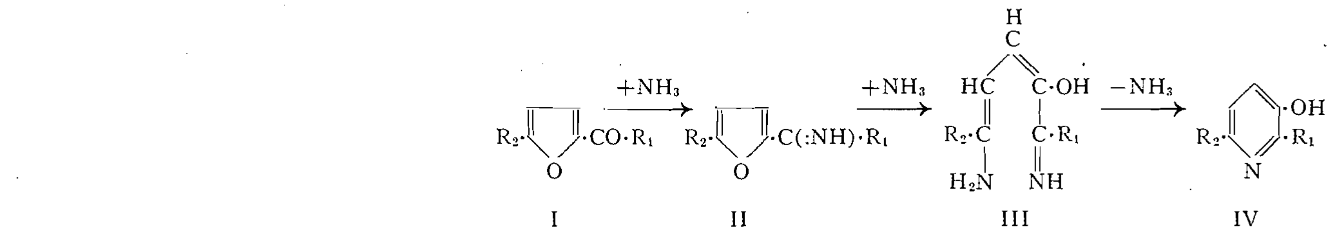
ABSTRACT

Aliphatic 2-furylketones rearrange to 3-hydroxy-2-alkylpyridines under the influence of ammonia and heat. The furylketones were prepared by a modified Friedel-Crafts reaction. Conditions to obtain the pyridine derivatives in good yield have been established.

A general method for the synthesis of 3-hydroxy-2-alkylpyridines is the Hofmann degradation of 2-alkylnicotinic acids as was shown by Dornow (1, 2, 3) who demonstrated this synthesis for 3-hydroxy-2-methylpyridine starting from 2-methylnicotinic acid made by the condensation of amino-crotonic ester and beta-ethoxyacrolein diethyl acetal. For the preparation of higher alkylated 3-hydroxypyridines, however, the starting material is more difficult to make, and the difficulties grow with the size of the side-chain. Recently Leditschke (11) has published a synthesis of 3-hydroxy-2-arylpyridines. The simplicity of his method and the good yields obtained suggested a similar procedure for the synthesis of aliphatic substituted pyridines, which are related to derivatives of previous (4, 5, 6) as well as current investigations.

The basic reaction of this synthesis is the rearrangement of 2-alkylfurylketones under the influence of ammonia:



The first step is the formation of the ketimine (II). Further addition of ammonia may bring about ring cleavage to (III), which is immediately transformed into the hydroxypyridine derivative (IV) with a simultaneous splitting off of ammonia. Direct proof of this mechanism is lacking because (III) has not been isolated. However, reaction products other than pyridine derivatives can be expected if primary amines are used instead of ammonia, because the last step (III) to (IV) takes place only with difficulty in the case of primary amines. Experiments have shown that under these conditions the reaction products are in fact not uniform.

The 2-alkylfurylketones used as starting materials were prepared by a Friedel-Crafts type reaction from furan and the corresponding acid anhydrides, using

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phosphoric acid or boron-trifluoride-etherate as a catalyst (9, 10). Some of these ketones are new (Table I).

TABLE I

No.	2-Furylketones (I)	B.p., °C., mm.Hg	Used method	Ref.
1	2-Acetylfuran ($R_1 = CH_3$, $R_2 = H$)	66–68° 11–12 mm.	A	7,8,9,10,12
2	2-Propionylfuran ($R_1 = C_2H_5$, $R_2 = H$)	63–65° 3–4 mm.	A	10
3	2-*n*-Butyrylfuran ($R_1 = n\text{-}C_3H_7$, $R_2 = H$)	75–77° 5–6 mm.	A	10
4	2-Isobutyrylfuran ($R_1 = \text{iso-}C_3H_7$, $R_2 = H$)	51–53° 3–4 mm.	A	
5	2-*n*-Valerylfuran ($R_1 = n\text{-}C_4H_9$, $R_2 = H$)	72–75° 2–3 mm.	B	
6	2-Isovalerylfuran ($R_1 = sec\text{-}C_4H_9$, $R_2 = H$)	67–70° 3–4 mm.	A	
7	2-*tert*-Valerylfuran ($R_1 = tert\text{-}C_4H_9$, $R_2 = H$)	57–60° 2–3 mm.	B	
8	2-Propionyl-5-methylfuran ($R_1 = C_2H_5$, $R_2 = CH_3$)	66–69° 2–3 mm.	A	
9	2-Phenacetylfuran ($R_1 = CH_2C_6H_5$, $R_2 = H$)	155–158° 2–3 mm.	C	

The rearrangement was best effected by heating the ketone with 2–3 moles of ammonia in alcoholic solution in a sealed tube at 170°C. for 15 hr. The ammonia solution was prepared by saturating absolute ethanol at 0°C. The presence of ammonium chloride increased the yields only slightly. The reaction mixtures were worked up by evaporating the alcohol under reduced pressure, distilling the residue *in vacuo*, and extracting a solution of the distillate in 2 *N* sodium hydroxide with chloroform to remove neutral contaminants. The alkaline solution of the hydroxypyridine was then neutralized and extracted again with chloroform. (Table II.)

While the rearrangement of 2-acetylfuran (I, $R_1 = CH_3$, $R_2 = H$) gave the 3-hydroxy-2-methylpyridine in a yield of only 4.6%, the yield increased rapidly with the size of R_1 and reached 74% for 3-hydroxy-2-propylpyridine (IV, $R_1 = C_3H_7$, $R_2 = H$, "*o*-hydroxyconyrine"). Equally satisfactory yields were obtained whether R_1 was straight or branched. The rearrangement of 2-benzylfurylketone (I, $R_1 = CH_2C_6H_5$, $R_2 = H$) under the same conditions gave a poor yield and Leditschke's method of heating the ketone with ammonium acetate at higher temperatures would seem advisable.

To investigate the behavior of a 5-alkyl substituted 2-furylketone, 5-methyl-2-propionylfuran (I, $R_1 = C_2H_5$, $R_2 = CH_3$) was treated by this procedure and yielded 85% of 3-hydroxy-2-ethyl-6-methylpyridine (IV, $R_1 = C_2H_5$, $R_2 = CH_3$).

The basic properties of these pyridine derivatives and their tendency to form picrates and chloroplatinates decrease with increasing size of the side-chain. All the compounds are readily soluble in 2 *N* acids and 1–2 *N* alkalies, and give a reddish-brown color reaction with ferric chloride in dilute alcoholic solution. Coupling with diazotized *o*- and *p*-nitroaniline gives brownish-red azo dyes.

TABLE II

No.	3-Hydroxy-2-alkylpyridines (IV)	M.p., °C.	Yield, %	Analytical figures	
				Calcd., %	Found, %
1	3-Hydroxy-2-methylpyridine ($R_1 = CH_3$, $R_2 = H$)	166–168	4.6	C_6H_7NO: N 12.84	12.6
	Picrate	203–205		N 16.57	16.8
	Chloroplatinate	160–163		Pt 29.57	29.62
2	3-Hydroxy-2-ethylpyridine ($R_1 = C_2H_5$, $R_2 = H$)	134–136	10	C_7H_9NO: N 11.37	11.5
	Picrate	173–175		N 15.91	16.0
3	3-Hydroxy-2-*n*-propylpyridine ($R_1 = n\text{-}C_3H_7$, $R_2 = H$)	133–135	74	$C_8H_{12}NO$: N 10.21	10.5
4	3-Hydroxy-2-isopropylpyridine ($R_1 = \text{iso-}C_3H_7$, $R_2 = H$)	191–192	81	C 70.04 H 8.08	70.04; 70.18 8.16; 8.02
5	3-Hydroxy-2-*n*-butylpyridine ($R_1 = n\text{-}C_4H_9$, $R_2 = H$)	127–129	78	$C_9H_{13}NO$: C 71.49 H 8.67	71.47; 71.30 8.64; 8.42
6	3-Hydroxy-2-*sec*-butylpyridine ($R_1 = sec\text{-}C_4H_9$, $R_2 = H$)	157–159	60	N 9.26	9.55
7	3-Hydroxy-2-*tert*-butylpyridine ($R_1 = tert\text{-}C_4H_9$, $R_2 = H$)	199–201	71		71.70; 71.45 8.71; 8.50
8	3-Hydroxy-2-ethyl-6-methylpyridine ($R_1 = C_2H_5$, $R_2 = CH_3$)	170–172	80	$C_8H_{11}NO$: C 70.04 H 8.08	69.78 8.06
9	3-Hydroxy-2-benzylpyridine ($R_1 = CH_2C_6H_5$, $R_2 = H$)	189–191	5.4	$C_{12}H_{11}NO$: C 77.81 H 5.99 N 7.56	77.46 5.72 7.55

The 3-hydroxy-3-methylpyridine was also prepared by Dornow's method so that a direct comparison of the products of both methods was possible. They were identical.

EXPERIMENTAL

Melting points are corrected. Analyses are by Drs. Weiler and Strauss, Oxford.

Method A. 2-Isopropylfurylketone (Table I, No. 4)

A well-stirred mixture of 95 gm. (0.6 moles) of isobutyric anhydride and 20.4 gm. (0.3 moles) of furan was warmed to 40°, the heat removed, and 6 gm. of 85% orthophosphoric acid was added at once. This caused a slight rise in temperature which was allowed to subside and the mixture was kept at 60° for two hours. After cooling, 120 ml. of water were added and the mixture stirred for one hour. The dark-colored organic layer was shaken for 24 hr. with saturated sodium carbonate solution. The ketone was taken up in chloroform, washed once with water, dried with anhydrous sodium sulphate, and the solvent removed under reduced pressure. The residue was distilled *in vacuo* twice through a short column. B.p. 51–53°C. (3–4 mm.), yield 40.0 gm., i.e. 93% based on furan.

Method B. 2-tert-Valerylfuran (Table I, No. 7)

A mixture of 37.2 gm. (0.2 moles) of trimethyl acetic anhydride and 12 gm. (0.177 moles) of furan was cooled in tap water to 15°C. and well stirred. Addition of 3 ml. of redistilled boron-trifluoride-etherate caused a slight rise of temperature. The mixture was kept at 60°C. for three hours, then cooled to 20° and, after adding 200 ml. of water, stirred for two hours. The ketone was taken up with chloroform, washed with 10% sodium carbonate solution, and, after removal of the chloroform, the product distilled *in vacuo* through a column. B.p. 57–60°C. (2–3 mm.) yield 22.0 gm., i.e. 91%.

Method C. 2-Benzylfurylketone (Table I, No. 9)

A mixture of 52 gm. (0.204 moles) of phenyl acetic anhydride, 11 gm. (0.162 moles) of furan, and 0.5 ml. of hydriodic acid (sp. gr. 1.7) was heated to 55°C. for three hours with good agitation. The heat was removed, 200 ml. of water added, and stirring was continued for two hours. The organic layer was drawn off and poured into 200 ml. of saturated sodium carbonate solution and allowed to stand for one week with occasional shaking. The ketone was taken up with chloroform and finally distilled *in vacuo*. B.p. 155–158°C. (2–3 mm.), yield 27.0 gm., i.e. 90%.

The following are a few typical examples of the rearrangement procedure.

3-Hydroxy-2-methylpyridine (Table II, No. 1)

Twelve grams of 2-acetylfuran and 30 ml. of a saturated solution of ammonia in absolute ethanol were heated with a trace of ammonium chloride in a sealed tube to 150°C. for 15 hr. After evaporating the alcohol under reduced pressure, the residue was digested with 100 ml. of 2 *N* sodium hydroxide solution, filtered through a wetted filter, and neutralized to litmus with 2 *N* hydrochloric acid. The mixture was extracted several times with chloroform, the solvent removed *in vacuo*, and the residue sublimed under a pressure of 0.1 mm. and 110–120°C. bath temperature. Final purification was by repeated crystallization from chloroform under pressure. M.p. 166–168°C., yield 0.560 mgm., i.e. 4.6% (based on 2-acetylfuran). Mixed with a sample prepared by degradation of 2-methylnicotinic acid according to (1), the melting point was not depressed. The *picrate* was prepared by adding an ethereal solution of the base to a solution of picric acid in ether, and the product was recrystallized from ether under pressure to give a yellow powder, m.p. 203–205°C. (dec.). The *chloroplatinate* was obtained by dissolving the base in the minimum amount of 20% hydrochloric acid and adding the calculated amount of chloroplatinic acid. The mixture was evaporated and the residue taken up in methanol and precipitated with ether. M.p. 160–163°C., very soluble even in methanol.

3-Hydroxy-2-ethylpyridine (Table II, No. 2)

Thirteen grams of 2-propionylfuran was sealed in a tube with 30 ml. of saturated alcoholic ammonia solution and heated at 160°C. for 15 hr. After cooling to room temperature there was an appreciable vacuum in the tube, showing the consumption of ammonia. After removal of the solvent, the residue was distilled *in vacuo*, after the forerun was rejected. The sublimated crystals were dissolved in 2 *N* sodium hydroxide (50 ml.) on the water bath and after cooling and diluting with an equal volume of water the solution was filtered and saturated with carbon dioxide. The base was extracted with chloroform and sublimed twice at 0.1 mm. and 120°C. (air bath). Recrystallization from chloroform–ether gave 1.132 gm., i.e. 9%, of white prisms, m.p. 134–136°C., reaction with ferric chloride in dilute alcoholic solution: dark red-brown. The *picrate* was made by mixing ethereal solutions of base and picric acid and recrystallizing from methanol–ether until a constant melting point of 173–175°C. (dec.) was reached; orange needles.

3-Hydroxyconyrine (Table II, No. 3)

2-*n*-Butyrylfuran, 11.6 gm., and 30 ml. of alcoholic ammonia solution were heated in a sealed tube to 165°C. for 20 hr. The product was worked up by evaporating the solvent and subliming the residue in a vacuum of 3 mm. almost without forerun. Yield, 8.5 gm. (i.e. 74%), m.p. 127–131°C. An analytical sample was prepared by recrystallization from a mixture of ether and petroleum ether and finally from ether alone, m.p. 133–135°C., thick prisms with the characteristic odor of the hemlock plant.

3-Hydroxy-2-benzylpyridine (Table II, No. 9)

2-Phenylacetylfuran, 13.7 gm., was heated with 30 ml. of ammonia solution in a sealed tube to 175°C. for 24 hr. The solvent was distilled off under diminished pressure leaving a liquid residue. Addition of ether produced a precipitate which was filtered off and discarded. The ethereal filtrate was treated first with 10% sodium bicarbonate solution, which was discarded, then five times with 50 ml. of 2 *N* sodium hydroxide solution which was separated and neutralized with 2 *N* hydrochloric acid. The neutral solution was extracted with ether, the solvent removed, and the remaining crystals sublimed in a vacuum of 1 mm. Recrystallization from ether under pressure yielded 0.734 gm. (i.e. 5.4%), m.p. 189–191°C.

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