ferrocene. Recrystallization from hexane gave red crystals m.p. 83–85°. Reported[2] 85°. Infrared maximum (carbonyl) 6.03 μ.

Acknowledgment. We would like to thank the Research Corp. for a Frederick Gardner Cottrell grant in support of this work.

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Synthesis of Some Heterocyclic Ketols by Ion-Exchange Resin Catalysis

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Received February 8, 1961

A series of heterocyclic ketols and their dehydration products, which were of interest to us because of their cardiovascular and tranquilizing properties, were prepared from the isomeric pyridinecarboxaldehydes and several *o*-hydroxyacetophenones. The use of conventional catalysts[2] such as sodium hydroxide[3–5] or piperidine[6,7] which have been employed in the condensation of heterocyclic aldehydes and ketones generally gave rather poor yields of the pyridalacetophenones. Frequently, large amounts of intractable, oily by-products were formed and only occasionally could any of the corresponding ketols be isolated. It appeared probable that the use of a basic catalyst, such as an ion-exchange resin, in a heterogeneous reaction medium might provide a more selective control over the course of the reaction and permit isolation of the desired ketols with a minimum of side reactions. In recent years a wide variety of reactions has been catalyzed by both anionic and cationic exchange resins[8,9] and the absence of a large excess of strong alkali is sometimes advantageous when sensitive compounds are being prepared.

We have found the strongly basic ion-exchange resin Amberlite IRA-400 (OH^-) in ethanol to give primarily the heterocyclic ketols accompanied in some instances by lesser amounts of the corresponding 2′-hydroxy-*trans*-pyridalacetophenones. The ketols which lost the elements of water most readily could not be isolated and were obtained either as the ketol hydrochlorides or were converted directly to their dehydration products. The ketol hydrochlorides were dehydrated in good yields to the corresponding pyridalacetophenones by simply warming in aqueous solution or, in other instances, by refluxing briefly in concentrated hydrochloric acid. While this investigation[10] was under way Raut and Wender[11] described the α,β-unsaturated ketones derived from 2- and 3-pyridinecarboxaldehyde and *o*-hydroxyacetophenone in the presence of aqueous-ethanolic potassium hydroxide and Corvaisier and Tirouflet[6b] reported the formation of the corresponding 2- and 4-ketols in the presence of sodium methylate.

When 3-pyridinecarboxaldehyde and *o*-hydroxyacetophenone were condensed in the presence of Amberlite IRA-400 (OH^-) and ethanol both the easily dehydrated ketol hydrochloride (2′,3-dihydroxy-3-(3-pyridyl)propiophenone hydrochloride, I) and the α,β-unsaturated ketone (2-hydroxy-β-(3-pyridyl)acrylophenone, Ia) were obtained. Compound I was dehydrated to Ia upon recrystallization from warm water or upon conversion to the ketol base and recrystallization from methanol.

The condensation of 2-pyridinecarboxaldehyde with *o*-hydroxyacetophenone under the same conditions gave the stable ketol (2′,3-dihydroxy-3-(2-pyridyl)propiophenone, II) and none of the dehydration product (2-hydroxy-β-(2-pyridyl)acrylophenone, IIa) was isolated. Compound II, however, was dehydrated to IIa by refluxing for a few minutes in concentrated hydrochloric acid. 4-Pyridinecarboxaldehyde reacted like the 2-isomer and with *o*-hydroxyacetophenone gave only the ketol (2′,3-dihydroxy-3-(4-pyridyl)propiophenone, III). The latter was dehydrated to the α,β-unsaturated ketone (2-hydroxy-β-(4-pyridyl)acrylophenone, IIIa) by refluxing in concentrated hydrochloric acid or by heating with polyphosphoric acid. In the presence of Dowex-3 (OH^-), a weakly basic ion-exchange resin, 4-pyridinecarboxaldehyde and *o*-hydroxyacetophenone gave only a trace of the ketol (III). When aqueous-ethanolic sodium hydroxide was used as the condensation catalyst the three isomeric pyridinecarboxaldehydes and *o*-hydroxyacetophenone gave the corresponding pyridalacetophenones.

3 - Pyridinecarboxaldehyde and 2 - hydroxy - 3-methoxyacetophenone in the presence of Amber-

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lite IRA-400 (OH^-) and ethanol formed the ketol (2′,3 - dihydroxy - 3′ - methoxy - 3 - (3 - pyridyl)-propiophenone, IV) but with 2-hydroxy-3,6-dimethoxyacetophenone the α,β-unsaturated ketone hydrochloride (2-hydroxy-3,6-dimethoxy-β-(3-pyridyl)acrylophenone hydrochloride, Va) was the principal product isolated from the reaction mixture. Prolonging the reaction time served only to convert a portion of Va to its cyclization product [2 - (3 - pyridyl) - 5,8 - dimethoxy - 4 - chromanone, Vb]. Compound IV also gave the cyclization product [2-(3-pyridyl)-8-methoxy-4-chromanone hydrochloride, IVb] upon treatment with concentrated hydrochloric acid. The reaction of 4-pyridinecarboxaldehyde with 2-hydroxy-3,6-dimethoxyacetophenone in the presence of the resin, on the other hand, paralleled that with *o*-hydroxyacetophenone and gave the ketol (2′,3-dihydroxy-3′,6′-dimethoxy - 3 - (4 - pyridyl)propiophenone, VI). Benzaldehyde and *o*-hydroxyacetophenone in the presence of Amberlite IRA-400 (OH^-) gave both 2′-hydroxychalcone and flavanone.

4 - Hydroxy - 4 - (2 - pyridyl) - 2 - butanone, which had been obtained in 41% yield from 2-pyridinecarboxaldehyde and acetone in the presence of sodium hydroxide,[5] was prepared in 70% yield when Amberlite IRA-400 (OH^-) was used as the condensation catalyst. The condensation products derived from the isomeric pyridinecarboxaldehydes with acetone and with acetophenone have been investigated by Marvel and co-workers.[4,5] These authors reported the ease with which the isomeric pyridyl ketols were dehydrated to increase as the substituent position in the heterocyclic ring was changed from 2 to 3 to 4. The differences were correlated with inductive effects of the nitrogen atom and with the ultraviolet spectra.[12] In our series it is of interest to note that the ketols derived from 3-pyridinecarboxaldehyde and *o*-hydroxyacetophenone were more readily dehydrated than their 2- or 4-isomers. Pietrzyk and co-workers[13] have studied the basic strengths of vinylpyridines, which may be viewed as simpler analogs of pyridalacetophenones, and pointed out the opposing effects of inductive and resonance forces. The enhanced resonance stabilization of 2′-hydroxypyridalacetophenones when compared with their unsubstituted analogs[12] is shown by a bathochromic shift of 6–12 mμ in the *trans*-chalcone band[14] of the ultraviolet spectrum. Furthermore, the infrared spectra exhibited carbonyl bands at approximately 1640 cm.$^{-1}$ which may be attributed to conjugated chelation of the *o*-hydroxyacetophenone residue.[15]

Thus, dehydration of the 2′-hydroxyketols appears to be controlled by resonance rather than inductive forces; the electron-withdrawing effect from the 2- and 4-positions of the pyridine ring by the nitrogen atom[16] opposes carbonium ion formation at the 2-carbon atom of the ketols and hinders dehydration to the pyridalacetophenones.

EXPERIMENTAL[17]

Preparation of the resin catalyst. Commercial Amberlite IRA-400 (Cl^-) was converted to the hydroxide cycle by gently stirring for 1 hr. with an excess of 5% aqueous sodium hydroxide solution. The resin was filtered off and washed repeatedly with distilled water until the filtrates were neutral. It was finally washed several times with ethanol and stored in the damp state in the refrigerator.

2′,3-Dihydroxy-3-(3-pyridyl)propiophenone hydrochloride (I). A solution of 10.7 g. (0.1 mole) of 3-pyridinecarboxaldehyde and 15.0 g. (0.11 mole) of *o*-hydroxyacetophenone in 100 ml. of ethanol and 20 g. of Amberlite IRA-400 (OH^-) were stirred gently at room temperature for 24 hr. Keto number titrations indicated that 80% of the aldehyde had reacted after 3 hr. and that after 24 hr. 98% of the aldehyde was consumed. The resin was filtered off and the clear, pale yellow filtrate was evaporated under reduced pressure below 50°. The residual oil was taken up in 1.5*N* hydrochloric acid and washed quickly with ether. Evaporation of the ether gave 3.6 g. of unchanged *o*-hydroxyacetophenone which was identified by its refractive index and infrared spectrum. The aqueous acid solution, which began to crystallize within a few minutes, was cooled in the refrigerator to give 11.0 g. (39%) of fine, cream-colored crystals, m.p. 181–182° dec. The analytical sample was obtained colorless without change in melting point when recrystallized from methanol. An additional 1.1 g., m.p. 181–182° dec., was extracted from the resin by washing with 1.5*N* hydrochloric acid. The carbonyl frequency exhibited a band at 1644 cm.$^{-1}$ in the infrared spectrum.

Anal. Calcd. for $C_{14}H_{14}NO_3Cl$: C, 60.11; H, 5.04; N, 5.01. Found: C, 60.22; H, 5.10; N, 5.10.

2-Hydroxy-β-(3-pyridyl)acrylophenone (Ia). The aqueous acid filtrate from which the ketol hydrochloride (I) had crystallized was neutralized with sodium bicarbonate and the precipitated oil was taken up in ether. Evaporation of the solvent and trituration of the amorphous, yellow residue with water gave 7.4 g. (33%) of a crystalline powder, m.p. 144–148°. Recrystallization from aqueous ethanol then yielded bright yellow crystals, m.p. 149–150° (reported[11] m.p. 161–162°). The ultraviolet spectrum exhibited a maximum at 305 mμ (ϵ 22,600); in the infrared the carbonyl band occurred at 1640 cm.$^{-1}$

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.40; H, 5.22; N, 6.15.

2′,3-Dihydroxy-3-(2-pyridyl)propiophenone (II). A solution of 10.7 g. (0.1 mole) of 2-pyridinecarboxaldehyde and 15.0 g. (0.11 mole) of *o*-hydroxyacetophenone in 100 ml. of ethanol and 20 g. of Amberlite IRA-400 (OH^-) was stirred gently in an ice bath. The ice melted during the next 2 hr. and stirring was continued at room temperature for 18 hr. longer. The resin was filtered off and the pale yellow filtrate

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was distilled under reduced pressure below 50°. The cooled liquid residue was taken up in 1.5N hydrochloric acid and washed with ether. Neutralization of the aqueous acid solution with sodium bicarbonate precipitated a yellowish oil which solidified in a short time. Recrystallization from methanol gave 10.0 g. (41%) of cream-colored crystals, m.p. 109–110°. The colorless analytical sample was obtained from heptane, m.p. 109–110° (reported[6b] m.p. 110°). The carbonyl band occurred at 1644 cm.$^{-1}$ in the infrared spectrum.

Extraction of the resin with 1.5N hydrochloric acid and cooling of the extract gave the hydrochloride of II, m.p. 170–171° dec. Upon neutralization with sodium bicarbonate the aqueous acid solution gave an additional 1.5 g. of the ketol, m.p. 108–110°.

2-Hydroxy-β-(2-pyridyl)acrylophenone (IIa). A solution of 2.0 g. of the ketol (II) in 10 ml. of concd. hydrochloric acid was refluxed for 3 min., cooled, and neutralized with sodium bicarbonate. The deep yellow precipitated oil gradually solidified. Recrystallization of the crude product (1.8 g., m.p. 80–84°) from aqueous methanol gave 1.4 g. (76%) of fine, bright yellow needles, m.p. 99–100° (reported[11] m.p. 101–102°). The ultraviolet spectrum exhibited a maximum at 309 mμ (ϵ 21,600) and in the infrared the carbonyl band occurred at 1635 cm.$^{-1}$

2′,3-Dihydroxy-3-(4-pyridyl)propiophenone (III). The condensation of 5.4 g. (0.05 mole) of 4-pyridinecarboxaldehyde and 7.5 g. (0.055 mole) of *o*-hydroxyacetophenone in the presence of 10 g. of the resin by the method employed for compound II gave 5.5 g. (45%) of almost colorless crystals, m.p. 143–146°. The analytical sample melted at 148–149° (from ethanol; reported[6b] m.p. 152°). The carbonyl band occurred at 1638 cm.$^{-1}$ in the infrared spectrum.

Approximately the same yield of the ketol (III) was obtained when the reaction was carried out in 60% ethanol. When the recovered resin was extracted with 1.5N hydrochloric acid an additional 1.0 g. of III separated in the form of its colorless hydrochloride, m.p. 206–207° (dec., from ethanol). Upon neutralization with sodium bicarbonate an aqueous solution of the latter gave III, m.p. 148–149° (from ethanol).

2-Hydroxy-β-(4-pyridyl)acrylophenone (IIIa). (a) A solution of 2.0 g. of the ketol (III) in 20 ml. of concentrated hydrochloric acid was dehydrated by procedure (a) for the preparation of compound IIa. Recrystallization of the crude product (1.7 g., m.p. 114–121°) from aqueous ethanol gave 1.1 g. of long, yellow needles, m.p. 124–125°. The ultraviolet spectrum exhibited a maximum at 292 mμ (ϵ 23,650); in the infrared the carbonyl band occurred at 1640 cm.$^{-1}$

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.68; H, 4.94; N, 6.08.

(b) One gram of the ketol (III) and 25 g. of polyphosphoric acid were heated at 100° with stirring for 5 min. The colorless solid dissolved with the formation of a deep orange solution and upon dilution with water and neutralization with sodium hydroxide it precipitated a yellow solid. Recrystallization of the crude product from ethanol gave 0.25 g. of bright yellow needles, m.p. 124–125°.

2′,3-Dihydroxy-3′-methoxy-3-(3-pyridyl)propiophenone (IV). A solution of 5.5 g. of 2-hydroxy-3-methoxyacetophenone[18] and 3.6 g. of 3-pyridinecarboxaldehyde was condensed in the presence of Amberlite IRA-400 (OH$^-$) and ethanol by the procedure employed for the preparation of compound II. The colorless solid which separated (1.8 g., m.p. 170–173° dec.) was obtained from aqueous ethanol as fine colorless needles, m.p. 173–175° dec.

Anal. Calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.75; H, 5.06; N, 5.42.

2-(3-Pyridyl)-8-methoxy-4-chromanone hydrochloride (IVb). When a solution of 100 mg. of compound IV in 2 ml. of concd. hydrochloric acid was refluxed for 1 min. and allowed to evaporate there remained a mass of colorless crystals, m.p. 235–236° (dec., from ethanol). The carbonyl band occurred at 1690 cm.$^{-1}$ in the infrared.

Anal. Calcd. for $C_{15}H_{14}NO_3Cl$: C, 61.75: H, 4.84. Found: C, 61.80; H, 5.04.

2-Hydroxy-3,6-dimethoxy-β-(3-pyridyl)acrylophenone hydrochloride (Va). A solution of 0.65 g. of 3-pyridinecarboxaldehyde and 1.0 g. of 2-hydroxy-3,6-dimethoxyacetophenone[19] in 10 ml. of ethanol was stirred gently for 24 hr. with 2.0 g. of Amberlite IRA-400 (OH$^-$). The resin was filtered from the orange solution and washed with ethanol. Distillation of the combined filtrates under reduced pressure on the steam bath left a deep orange liquid which was taken up in dilute hydrochloric acid and washed with ether. Neutralization of the aqueous acid solution precipitated an orange semisolid which was dissolved in ether. The ether phase was dried by shaking briefly with anhydrous magnesium sulfate and acidified slightly by passing a stream of anhydrous hydrogen chloride over the surface of the solution. The dense, deep red precipitate which separated (0.99 g., m.p. 229–231° dec.) was recrystallized from ethanol, m.p. 233–234° dec. The carbonyl band occurred in the infrared at 1642 cm.$^{-1}$

Anal. Calcd. for $C_{16}H_{16}NO_4Cl$: C, 59.54; H, 5.31; N, 4.34. Found: C, 59.47; H, 5.07; N, 4.41.

When the reaction time was extended to 72 hr., compound Va and a colorless by-product were obtained in approximately equal yields. The colorless material [2-(3-pyridyl)-5,8-dimethoxy-4-chromanone, Vb] melted at 173–174° (dec., from ether). It was insoluble in dilute sodium hydroxide solution and the carbonyl band occurred at 1695 cm.$^{-1}$ in the infrared.

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.17; H, 5.44; N, 4.76.

2′,3-Dihydroxy-3′,6′-dimethoxy-3-(4-pyridyl)propiophenone (VI). The condensation of 2.6 g. of 4-pyridinecarboxaldehyde and 4.9 g. of 2-hydroxy-3,6-dimethoxyacetophenone by the procedure employed for compound II gave 0.5 g. of colorless crystals, m.p. 124–125° (from ethanol).

Anal. Calcd. for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.30; H, 5.53; N, 4.75.

4-Hydroxy-4-(2-pyridyl)-2-butanone. A solution of 5.2 g (0.05 mole) of 2-pyridinecarboxaldehyde in 100 ml. of acetone was cooled in a Dry Ice bath and 10 g. of the resin was added. The suspension was stirred gently for 24 hr. in the cold and allowed to warm to room temperature. The resin was filtered off and the filtrate was concentrated under reduced pressure on the steam bath. The residue of pale orange liquid, which solidified to an oily crystalline mass (8.7 g.), was recrystallized from heptane to yield 5.4 g. (70%) of colorless crystals, m.p. 75–76° (reported[5] m.p. 75.5–76°).

The hydrochloride melted at 120–121° (from ethanol-ethyl acetate).

Anal. Calcd. for $C_9H_{12}NO_2Cl$: C, 53.34; H, 5.97; N, 6.91. Found: C, 53.09; H, 6.00; N, 7.06.

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Reactions of *N*-Chloromethylphthalimide with Nucleophilic Divalent Sulfur Compounds

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Received February 13, 1961

The reactions of *N*-bromomethylphthalimide with various nucleophilic reagents have been re-