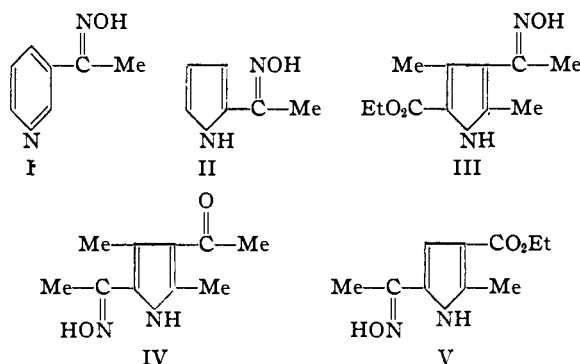


[COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Preparation of Derivatives of Pyrrole and Pyridine by Hydrogenation

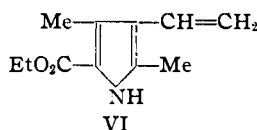
BY HOMER ADKINS, IVAN A. WOLFF, ALBERT PAVLIĆ AND ELMER HUTCHINSON

The hydrogenation of oximes to amines of the type $RCHNH_2CH_3$, where R is a pyridyl or pyrrolyl radical, has not hitherto been reported. Five oximes, I to V, have been prepared and submitted to hydrogenation over Raney nickel.



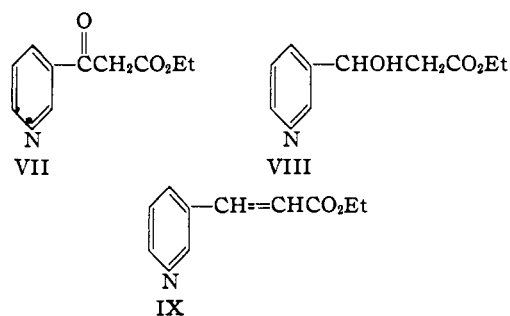
The five oximes reacted rapidly with hydrogen at 110 to 150°. I, II and III like simple ketoximes^{1,2} gave the corresponding primary amines. The oximes IV and V underwent hydrogenolysis, the $-C=NOH$ group being converted to $-CH_2CH_3$ in yields of 36 and 95%, respectively.

The oxime, I, gave a 74% yield of primary, and 11% yield of secondary amine; II and III gave primary amines, isolated as the benzoyl derivatives, in yields of 56 and 80%, respectively. The amines from II and III could not be isolated as such for, on distillation of the reduction products, resinification or decomposition occurred. Distillation of the product from (III) gave a 55% yield of the deamination product (VI) and this result suggests that the reduction of an oxime followed by deamination may offer a practical method of converting an acetyl group to a vinyl group.



An end result similar to the above deamination was observed on hydrogenating β -nicotinyl-acetic ester (VII). The hydrogenation went smoothly but attempts to purify the product gave not the hydroxy ester (VIII) but the unsaturated ester (IX).

The hydrogenolysis of the oximino group in IV before the acetyl group reacted is not surprising



since a carbonyl group in the α -position in pyrrole is much more reactive than in the β -position. For example, both hydrogen³ and hydroxylamine reacted first with the acetyl group in the 5-position in 2,4-dimethyl-3,5-diacetylpyrrole.

The hydrogenation of β -cyanopyridine, X, went rather smoothly to give a 42% yield of β -pyridylmethylamine XI, and a 48% yield of the corresponding secondary amine $(C_5H_4NCH_2)_2NH$.



The hydrogenations of the oximes and the nitrile and ketone noted above are characterized by the fact that hydrogenation of the oximino or cyano or carbonyl group or hydrogenolysis of an amino group took place preferentially as contrasted with the hydrogenation of a pyridine or pyrrole ring. Hydrogenolysis of an amino group did not occur when it was γ to the nitrogen of the cycle as in I and III. However, when the amino group was β to the nitrogen of the ring, it was in part, as in II, or completely, as in IV and V, eliminated by hydrogenolysis.

An amino group in the α -position to the ring did not undergo hydrogenolysis so readily as did a hydroxyl group in the same position. Thus, it is possible to prepare amines of the type $RCHNH_2CH_3$, where R is an α or β -pyrrole radical, while the corresponding alcohols are so susceptible to hydrogenolysis that they have never been prepared by a catalytic method. Thus, the ketone corresponding to III was almost quantitatively converted to 2,4-dimethyl-3-ethyl-5-carbethoxy-pyrrole. This is a general reaction for acetylpyrroles.

Dehydration of alcohols of the type $RCHOHCH_2-$ and deamination of amines of the type $RCHNH_2CH_2-$, where R is pyridyl or pyrrolyl took place readily.

(1) Winans and Adkins, *THIS JOURNAL*, **55**, 2051 (1933).(2) Smith and Adkins, *ibid.*, **60**, 660 (1938).(3) Signaigo, Rainey and Adkins, *ibid.*, **58**, 709 (1936); **61**, 1104 (1939).

Experimental Part

β -Cyanopyridine.—Nicotine was oxidized to nicotinic acid⁴ and the latter converted to the nitrile by heating it with ammonium acetate and acetic acid. A mixture of 0.5 mole of nicotinic acid (61.5 g.), one mole of ammonium acetate (77 g.) and 0.5 mole of acetic acid (30 g.) was heated under a Widmer column without a spiral,² at such a rate that about 60 ml. of distillate came over within an hour, when the temperature at the head of the column was 142°. The water condenser was replaced with an air condenser and an additional 70 ml. slowly distilled during the ensuing hour, the temperature at the head of the column rising to 180°. The distillate was made alkaline with ammonium hydroxide and cooled to -8°. A portion of the nitrile crystallized and the remainder was extracted with ether. The nitrile was distilled at about 105° (30 mm.). The yield was 21 to 23 g., m. p. 52-52.5°.

The method described above is much more satisfactory than that in which the acid is successively converted to the ester, the amide and the nitrile.⁵ Apparently there is a misprint in LaForge's paper where it is stated that 19.5 to 20.5 g. of the nitrile was obtained from 18 g. of the amide.

2-Acetylpyrrole.—Pyrrole (177 g.) in 400 ml. of dry ether was added to a solution of a Grignard reagent from three moles of ethyl bromide. The mixture was heated with stirring for a half hour and cooled in an ice-bath. Acetyl chloride (207 g.), which had been distilled from dimethylaniline and dissolved in 450 ml. of dry ether, was added slowly to the solution of the Grignard reagent of pyrrole. The mixture was then allowed to stand overnight. Ice was added to the reaction mixture and the ether distilled. The mixture was then subjected to steam distillation until four liters of water were collected. 2-Acetylpyrrole (80 g.), m. p. 88-89°, crystallized from the first three liters of distillate, while 46 g. was obtained by extraction with ether of the mother liquors and the fourth liter of distillate.

The 2-acetylpyrrole (40 g.) and hydroxylamine hydrochloride (40 g.) were heated together with 80 g. of hydrated sodium acetate, 700 ml. of water and 100 ml. of 95% ethyl alcohol, for seventy-five minutes on a steam-bath. The oxime (35.8 g.) crystallized when the reaction mixture was allowed to stand in a refrigerator overnight. After recrystallization from water the m. p. was 144-145°. The sample used for hydrogenation was not recrystallized.

2,4-Dimethyl-3-acetyl-5-carbethoxypyrrrole was prepared in 55% yield by the condensation of 348 g. of acetylacetone with oximinoacetoacetic ester (from 402 g. of acetoacetic ester) in the presence of 450 g. of zinc dust and 1200 ml. of acetic acid.⁶ The pyrrole (100 g.) so prepared was refluxed for three hours with 100 g. of hydroxylamine hydrochloride, and 200 g. of hydrated sodium acetate dissolved in 350 ml. of water and 1250 ml. of 95% alcohol. After the completion of the reaction, the volume of the mixture was reduced to about 800 ml. by distillation. The oxime was then precipitated by the addition of water. After recrystallization from methanol, the yield was 70 to 80 g., m. p. 197-198°.

2,4-Dimethyl-3-carbethoxy-5-acetylpyrrole was made by the interaction of the oximino ketone from 83 g. of acetylacetone and 108 g. of acetoacetic ester as in the preceding preparation. The yield was only 23%, as contrasted with the 74% yield obtained by the catalytic method.⁷ A 96% yield of the oxime, m. p. 161-163°, was obtained by refluxing the ketone (36 g.), hydroxylamine hydrochloride (54 g.), hydrated sodium acetate (108 g.), water (360 ml.) and 95% ethyl alcohol (360 ml.) for twelve hours. Water was then added to the solution until the oxime began to separate. The oxime was then allowed to crystallize.

2,4-Dimethyl-3,5-diacetylpyrrole was obtained in 30% yield as by Fischer and Neber.⁸ The oxime was prepared as from the 2,4-dimethyl-3-carbethoxy-5-acetylpyrrole,

except that the period of reaction was only fifteen minutes. In order to bring about the crystallization of the oxime from the reaction mixture, it was necessary to add water. An 85% yield of the oxime, m. p. 240° (dec.), was obtained.

Ethyl nicotinoacetate and β -acetylpyridine were made by methods previously described.^{9,10,11} The yield of the keto ester, as the hydrochloride, was about 60% and of β -acetylpyridine 96%. The oxime of acetylpyridine was prepared in 67% yield by the method described above. The oxime was extracted with ether from the reaction mixture after it was made alkaline with sodium carbonate. After the evaporation of the ether the crude oxime was crystallized from benzene, m. p. 116-117°.

Hydrogenations.—In general, approximately 0.1 mole of compound dissolved in 100 ml. of dioxane or dry ethyl alcohol was hydrogenated over 2 to 3 g. of Raney nickel under 200 atm. of hydrogen.

The oxime of acetylpyridine (20.4 g.) took up two moles of hydrogen per mole of oxime within forty-five minutes at 100°. Fractional distillation gave 13.6 g., b. p. 112-113° (22 mm.), of 3-(α -aminoethyl)-pyridine, n_D^{25} 1.5285, d_4^{25} 1.014. The phenylthiourea of the amine had a m. p. of 139-140° and the picrate m. p. 204-205°.

The oxime of 2-acetylpyrrole took up two moles of hydrogen per mole of oxime within thirty minutes at 130°. All attempts to distill the product caused resinification and decomposition. Benzoyl chloride (25 ml.) was added to the product of hydrogenation of 12.4 g. of the oxime in dioxane to which 500 ml. of water and 30 g. of sodium hydroxide had been added. The mixture was stirred for an hour and allowed to stand overnight. The benzoate of 2-(α -aminoethyl)-pyrrole (12.1 g.) separated out, and upon recrystallization from benzene gave 6.4 g. of a pure fluffy white compound, m. p. 149-150°.

The oxime of 2,4-dimethyl-3-acetyl-5-carbethoxypyrrrole behaved upon hydrogenation exactly as did the oxime of 2-acetylpyrrole. The benzoyl derivative of 2,4-dimethyl-3-(α -aminoethyl)-5-carbethoxypyrrrole was obtained by a process similar to that described above. The yield of crude benzoate was 25.1 g. from 22.4 g. of the oxime. Upon recrystallization from benzene 12.6 g. of pure benzoyl derivative, m. p. 179-180°, was obtained.

There was obtained by the distillation of the product of the hydrogenation of the oxime 13.4 g. of a compound, which after recrystallization from 70% ethyl alcohol, showed a b. p. of 145-148 (3 mm.), and a m. p. of 110.5-112°. These physical constants correspond to those of 2,4-dimethyl-3-vinyl-5-carbethoxypyrrrole.¹² The identity of the compound was further established by hydrogenating it over Raney nickel at 100° to 2,4-dimethyl-3-ethyl-5-carbethoxypyrrrole.

The monoxime of 2,4-dimethyl-3,5-diacetylpyrrole (formula IV) absorbed approximately four moles of hydrogen per mole of oxime within thirty minutes at 140-150°. However, the only pure product that was isolated, by distillation or attempts to form a benzoyl derivative, was a 30 to 36% yield of 2,4-dimethyl-5-ethyl-3-acetylpyrrole, m. p. 106-107°. The latter was isolated readily by diluting the reaction mixture to two liters with water.

2,4-Dimethyl-3-acetyl-5-carbethoxypyrrrole took up 2 moles of hydrogen within one and one-half hours at 170° to give 2,4-dimethyl-3-ethyl-5-carbethoxypyrrrole in 95% yield. The oxime of 2,4-dimethyl-3-carbethoxy-5-acetylpyrrole gave a 94% yield of 2,4-dimethyl-3-carbethoxy-5-ethylpyrrole after hydrogenation for 15 minutes at 130°.

β -Cyanopyridine (20 g.) took up 2 moles of hydrogen per mole of nitrile within thirty to 45 minutes at 130°. Fractional distillation gave two products: 8.6 g. of β -pyridylmethylamine, n_D^{25} 1.5485, d_4^{25} 1.062, b. p. 104-107 (14 mm.) or 112-113 (18 mm.), 9.2 g. of di- β -pyridylmethylamine, n_D^{25} 1.5696, d_4^{25} 1.128, b. p. 170-171° (2 mm.). Three solid derivatives of the primary amine were prepared:

(4) McElvain, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1932, Col. Vol. I, p. 378.

(5) LaForge, *THIS JOURNAL*, **50**, 2477 (1928).

(6) Fischer, Baumann and Riedl, *ibid.*, **475**, 238 (1929).

(7) Winkler and Adkins, *THIS JOURNAL*, **55**, 4167 (1933).

(8) Fischer and Neber, *ibid.*, **496**, 25 (1932).

(9) Strong and McElvain, *THIS JOURNAL*, **55**, 816 (1933).

(10) Adkins, Kuick, Farlow and Wojcik, *ibid.*, **57**, 2425 (1935).

(11) Kuick and Adkins, *ibid.*, **57**, 143 (1935).

(12) Fischer-Orth, "Die Chemie des Pyrrols," Akademische Verlagsgesellschaft M. B. H., Leipzig, 1931, p. 221.

TABLE I
PHYSICAL CONSTANTS AND ANALYTICAL DATA

Compound	B. p. or m. p., °C.	Formula	Analyses, %	
			Calcd.	Found
β -Pyridyl-methylamine ¹³	112 (18 mm.)	C ₆ H ₈ N ₂	N, 25.93	26.06
Picrate ^{13,14}	210-211 dec.	C ₁₂ H ₁₁ N ₅ O ₇		
3-(α -Aminoethyl)-pyridine ¹⁴	223 (740 mm.) 112-113 (22 mm.)	C ₇ H ₁₀ N ₂	N, 22.95	23.12
Phenylthiourea	139-140	C ₁₄ H ₁₆ N ₂ S	N, 16.34	16.29
Chloroplatinate	280 dec.	C ₇ H ₁₀ N ₂ ·H ₂ PtCl ₆	Pt, 36.68	36.66
Picrate	204-205	C ₁₂ H ₁₃ N ₅ O ₇	N, 19.31	19.46
Di-(β -pyridylmethyl)-amine	147-148 (mm.)	C ₁₂ H ₁₃ N ₃	N, 21.11	20.81
Chloroplatinate	>300	C ₁₂ H ₁₃ N ₃ ·H ₂ PtCl ₆	Pt, 35.96	35.68
Picrate	218-220	C ₁₈ H ₁₆ N ₆ O ₇	N, 18.96	18.80
[Di- α, α' -(3-pyridyl)]-diethylamine	152-153 (1 mm.)	C ₁₄ H ₁₇ N ₂		
Chloroplatinate	292, 161-163	C ₁₄ H ₁₇ N ₂ ·H ₂ PtCl ₆	Pt, 34.76	34.64
Picrate	205 dec.	C ₂₀ H ₂₀ N ₆ O ₇	N, 18.38	18.56
Oxime of 2,4-dimethyl-3-acetyl-5-carbethoxypyrrole	197-198	C ₁₁ H ₁₆ N ₂ O ₃	N, 12.50	12.47
Oxime of 2,4-dimethyl-3-carbethoxy-5-acetylpyrrole	162-163	C ₁₁ H ₁₆ N ₂ O ₃	N, 12.50	12.63
Monoxime of 2,4-dimethyl-3,5-diacetylpyrrole	240 dec.	C ₁₀ H ₁₄ N ₂ O ₂	N, 14.43	14.08
2,4-Dimethyl-3-vinyl-5-carbethoxypyrrole	110.5-112	C ₁₁ H ₁₅ NO ₂	N, 7.25	7.57
Benzoate of 2,4-dimethyl-3-(α -aminoethyl)-5-carbethoxypyrrole	179-180	C ₁₈ H ₂₂ N ₂ O ₃	N, 8.92	9.01
Benzoate of 2-(α -aminoethyl)-pyrrole	149-150	C ₁₃ H ₁₃ N ₂ O	N, 13.08	12.91
2,4-Dimethyl-3-acetyl-5-ethylpyrrole	159-160	C ₁₀ H ₁₆ NO	N, 8.48	8.58
2,4-Dimethyl-3-carbethoxy-5-ethylpyrrole	106-107	C ₁₁ H ₁₇ NO ₂	N, 7.18	7.38
Ethyl β -(3-pyridyl)-acrylate hydrochloride	186-187	C ₁₀ H ₁₁ NO ₂ ·HCl	C, 56.20 H, 5.62 Cl, 16.65	56.35 5.78 16.62

a picrate, m. p. 210-211° dec., a dihydrochloride, m. p. 222°, and a *p*-nitrobenzoate, m. p. 188-189°. The picrate of the secondary amine had a m. p. of 218-220°.

Ethyl nicotinoacetate (30 g.) took up 1 mole of hydrogen per mole of ester at 85° within two and one-half hours. Fractional distillation of the product gave 11 g. of a compound, b. p. 136-138° (3 mm.), believed to be β -(3-pyridyl)-acrylate ester. The ester polymerized so rapidly that within twenty-four hours the refractive index had fallen from 1.5518 to 1.4612; however, a stable hydrochloride, m. p. 185-186°, was obtained.

Summary

The hydrogenations over Raney nickel of eight oximino, keto and cyano derivatives of pyrrole and pyridine have been described.

(13) Craig and Hixon, *THIS JOURNAL*, **53**, 4369 (1931).

(14) Erlenmeyer and Epprecht, *Helv. Chim. Acta*, **20**, 690 (1937).

MADISON, WISCONSIN

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF SPRAGUE ELECTRIC CO.]

Preparation of Substituted Styrenes

BY LESTER A. BROOKS

Our interest in a study of the electrical characteristics of the polymers of various halogen substituted styrenes has necessitated the preparation of the corresponding monomers. Since the results of the electrical measurements are not complete and will be reported in a later paper, we are describing the preparation of several monomeric styrene derivatives at this time.

A knowledge of the electrical properties of materials is of value in the communications field and considerable work has been reported on various organic compounds.^{1,2,3} However, it appears that

little investigation has been made of specific styrene derivatives.

A modification of the styrene molecule accomplished by the introduction of a halogen atom in the ring will raise the dielectric constant. Any advantage due to increased dielectric constant will be nullified if a correspondingly large increase in dielectric loss occurs, or if the resulting polymer is not chemically stable in an electric field. It is well known that many iodine compounds are thermally unstable even at moderate temperatures. Bromine compounds also show this behavior but to a less extent, as, for example, in the case of the isomeric polybromostyrenes.⁴

(1) White and Bishop, *THIS JOURNAL*, **62**, 8 (1940).

(2) White, Biggs and Morgan, *ibid.*, **62**, 16 (1940).

(3) Mead and Fuoss, *ibid.*, **65**, 2067 (1943).

(4) Marvel and Moon, *ibid.*, **62**, 45 (1940).