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# Pyrrole chemistry. VIII. By-products in the synthesis of 2-pyrrolecarbonitrile

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Two by-products are formed when 2-pyrrolecarbonitrile is prepared by the acetic anhydride dehydration of 2-pyrrolecarbaldoxime. These have been proved to be 2-acetamidocarbonylpyrrole and 1-acetyl-2-pyrrolecarbonitrile. The latter acts as an acetylating agent.

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An earlier paper in this series (1) reported the synthesis of 2-pyrrolecarbonitrile by the dehydration of 2-pyrrolecarbaldoxime using hot acetic anhydride. Subsequently, in the course of large scale preparations of the nitrile, we obtained two by-products. One of these, a highmelting solid from the residue after vacuum distillation, was also reported by Fournari and Tirouflet (2) who prepared the nitrile by the same method. On the basis of the elemental analysis and polarographic behavior they suggested it to be the acetylated oxime. The second by-product was a solid whose much lower melting point was close to that reported by Fischer and Orth (3) for a compound which they obtained by heating the 2-aldoxime with acetic anhydride and sodium acetate. These authors assigned to it the structure 5-acetyl-2-pyrrolecarbonitrile (a-acetyl-a'-cyanopyrrole) but advanced no evidence other than elemental analysis.

The nuclear magnetic resonance (n.m.r.) and infrared spectra of our lower-melting nitrile by-product suggested it to be 1-acetyl-2-pyrrolecarbonitrile. It could be prepared very easily by the action of acetic anhydride on the 2-nitrile in the presence of triethylamine. The synthesis of Fischer and Orth was then repeated and found to give only this same compound. However, it seemed possible that those authors might have obtained the 5-acetyl compound, not otherwise recorded in the literature, and that it could possibly have nearly the same melting point as the 1-acetyl-2-nitrile.

It had been shown earlier (4) that the Friedel– Crafts acetylation of 2-pyrrolecarbonitrile gave only the 4-acetyl-2-nitrile. However, the action of a catalytic amount of perchloric acid on a solution of the 2-nitrile in acetic anhydride and acetic acid gave a mixture of the 4-acetyl and 5-acetyl derivatives from which the much more soluble 5-acetyl-2-nitrile was separated by extraction. The structure of this isomer was confirmed by elemental analysis, n.m.r., and infrared spectra. It was quite different from the low-melting 1-acetyl derivative obtained above and consequently could not have been the compound obtained by Fischer and Orth.

From the ease of formation it appeared likely that 1-acetyl-2-pyrrolecarbonitrile would act as an acetylating agent. It was found that refluxing this compound in benzene with an equimolar quantity of aniline produced a 33% conversion to acetanilide. No attempt has yet been made to find the best conditions for this reaction.

The n.m.r. spectrum of the high-melting byproduct appeared consistent with the acetylated oxime structure suggested by Tirouflet and Fournari while the infrared spectrum was not conclusive. It seemed possible that the product was the acetylated syn oxime arising from the difference in the ease of dehydration of the syn and anti forms. The presence of a small amount of the syn oxime, which should not dehydrate as easily as the anti (5), might result in some surviving the reaction in the acetylated form. However, a purified sample of the more easily obtained *anti* form was acetylated in the cold to the rather unstable O-acetyl-2-oxime and the infrared spectrum was found to be quite different from that of the high-melting by-product. In addition, this acetylated oxime decomposed very easily. These observations excluded the possibility that the structure could be that of an acetylated oxime in either form.

The n.m.r. splittings of the aromatic protons of the high-melting by-product indicated only a single attachment at the 2-position of the pyrrole ring, an acetyl group, and another acidic proton of the NH type.

This evidence suggested a  $-CO-NH-CO-CH_3$  side chain, consistent with the infrared

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spectrum which showed two carbonyl bands. It did not seem likely that acetylation of 2-pyrrolecarboxamide, formed by partial hydrolysis of the nitrile, could have occurred. Acetylation of the pyrrole nitrogen of that compound would be much more likely than attack on the amide nitrogen. An attempted synthesis of 2-acetamidocarbonylpyrrole by acetylation of the amide failed to give the desired product. A possible mode of formation of the suggested side chain would be a Beckmann rearrangement in which the O-acetylated oxime rearranged to the Nacetylated amide. There appears to be general agreement that both the dehydration of aldoximes and the Beckmann rearrangement proceed through O-acetylated oxime intermediates (6). However, while nitriles generally arise in the Beckmann rearrangement of aldoximes, the normal conditions for nitrile formation do not appear to produce amides as by-products (7). There are a few examples where O-acyloximes have been rearranged to N-acylamides (8); however, none was an aldoxime rearrangement.

A possible approach to the synthesis of substituted amides is through the attack of isocyanates on the pyrrole ring (9). This would require the use of acetyl isocyanate, first prepared by Billeter (10). That reagent was prepared in benzene solution and pyrrole was added directly to it. The product, when purified, was found to be identical to the high-melting byproduct through comparison of its infrared spectrum and a mixture melting point.

Thus the two by-products from the acetic anhydride dehydration of 2-pyrrolecarbaldoxime are 1-acetyl-2-pyrrolecarbonitrile and 2-acetamidocarbonylpyrrole.

#### General

Melting points are uncorrected. Elemental analyses were determined by Alfred Bernhardt, Mülheim (Ruhr), Germany.

Experimental

Infrared spectra were recorded on a Perkin-Elmer 237B spectrophotometer by the potassium chloride disc, solution (chloroform, 0.5 mm NaCl cell), or paraffin mull techniques.

The nuclear magnetic resonance spectra were determined on a Varian A-60 spectrometer at 60 Mc.p.s. The chemical shifts are in parts per million from tetramethyl-silane as internal reference and are recorded on the  $\delta$  scale. The proton on the pyrrole ring nitrogen was decoupled by the addition of a few drops of deuterium oxide.

# NOTES

## Isolation of the By-products

2-Pyrrolecarbaldoxime (22 g, 0.24 moles) was heated with acetic anhydride (60 ml) and the product worked up in the usual manner (1). The vacuum distillate was then fractionated several times until the nitrile, b.p. 80-82° at 1 mm, was shown to be pure by gas-liquid chromatography. The higher boiling material, 111-135° at 4 mm, partly crystallized on standing and was recrystallized from ethanol-water and then water to give about 200 mg 1-acetyl-2-pyrrolecarbonitrile, m.p. 74-74.5°. (Fischer and Orth (3) reported m.p. 74-75° for their  $\alpha$ -acetyl- $\alpha'$ cyanopyrrole.) Infrared carbonyl 1740 cm<sup>-1</sup> and nitrile 2220 cm<sup>-1</sup> (chloroform). Nuclear magnetic resonance: H-3, 7.02; H-4, 6.36; H-5, 7.42;  $J_{3,5}$  1.46;  $J_{3,4}$  3.45;  $J_{4,5}$ 3.24 c.p.s. (chloroform-d).

Anal. Calcd. for  $C_7H_6N_2O$ : C, 62.67; H, 4.51; N, 20.88. Found: C, 62.56; H, 4.52; N, 21.07.

A solid was recovered by successive extraction with boiling water of the black residue after vacuum distillation. Several recrystallizations, with decolorizing, from water and then from isopropyl alcohol gave about 750 mg of 2-acetamidocarbonylpyrrole, m.p. 219–219.5°; (lit. m.p. 218° (2)). Infrared carbonyls 1700 cm<sup>-1</sup> and 1650 cm<sup>-1</sup> (paraffin mull). Nuclear magnetic resonance: H-3, 7.08; H-4, 6.16; H-5, 7.22 (dimethyl sulfoxide- $d_6$ ). Sample solubility too low to determine coupling constants.

Anal. Calcd. for C<sub>7</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.18; H, 5.25; N, 18.28.

#### *I-Acetyl-2-pyrrolecarbonitrile*

This compound was synthesized in nearly quantitative yield by the action of acetic anhydride on 2-pyrrolecarbonitrile in the presence of triethylamine. It was the only product when the 2-nitrile was refluxed in acetic anhydride - acetic acid. It formed in about 60% yield when 2-pyrrolecarbaldoxime was treated with acetic anhydride and triethylamine. No heat was necessary for this reaction beyond that which it developed. The synthesis of Fischer and Orth (3) was repeated and the product isolated according to their directions. The yield was about 35%. It was established that the same compound was produced from each of these reactions and that it was identical to the lower-melting by-product obtained above through the identity of infrared spectra in KCl discs and in chloroform solution as well as through a series of mixture melting points.

#### Acetylation of Aniline

A solution of 1-acetyl-2-pyrrolecarbonitrile (0.83 g) and aniline (0.57 g) in 10 ml benzene was refluxed for 5 h. The cold product was washed with 3 ml 6 N hydrochloric acid, 3 ml 10% sodium hydroxide, and with 3 ml water. After evaporation the oily solid was dissolved in ether and again washed with 10% sodium hydroxide solution, dried, and evaporated. The solid was recrystallized from benzene-cyclohexane to give 0.27 g (33%) acetanilide. The identity of the product was confirmed by the infrared spectrum and mixture melting point with an authentic sample.

### The C-Acetylation of 2-Pyrrolecarbonitrile

2-Pyrrolecarbonitrile (0.5 g) was dissolved in a mixture of acetic acid (4 ml) and acetic anhydride (2 ml). To this

solution 5-6 drops of perchloric acid (70%) was added and the mixture swirled. After the reaction ceased the solution was poured into about 50 g of ice and water with stirring and allowed to hydrolyze. The buff solid was filtered (0.33 g) and the mother liquor saturated with salt and extracted three times with ether. When all the solvent was removed by flash evaporation a further 0.22 g was obtained. Finally, by making the mother liquor basic and extracting again, 0.13 g was obtained. The total crude product recovered was about 94% of theory, assuming monoacetylation. Extraction of the crude solid with cold ether, evaporation, then extraction of the recovered solid with cold chloroform and evaporation gave about 0.15 g (20%) of 5-acetyl-2-pyrrolecarbonitrile, m.p. 154.5-155.5° from benzene-cyclohexane. Infrared carbonyl 1655 cm<sup>-1</sup> and nitrile 2220 cm<sup>-1</sup> (chloroform). Nuclear magnetic resonance: H-3, 7.08; H-4, 7.00; J<sub>3,4</sub> 3.80 c.p.s. (dimethyl sulfoxide- $d_6$ ).

Anal. Calcd. for  $C_7 H_6 N_2 O$ : C, 62.67; H, 4.51; N, 20.88. Found: C, 62.76; H, 4.65; N, 21.03.

The very much less soluble isomer was identified, through mixture melting point and infrared spectrum of a purified sample, as the known (4) 4-acetyl-2-pyrrolecarbonitrile.

#### The O-Acetyl Derivative of Anti-2-pyrrolecarbaldoxime

A pure sample of the anti form of 2-pyrrolecarbaldoxime, (20 mg) m.p. 165-167° (lit. m.p. 165-166° (11)) was prepared. Infrared NH at 3440 cm<sup>-1</sup>, OH at 3560 cm<sup>-1</sup>, C=N at 1640 cm<sup>-1</sup> (chloroform). Nuclear magnetic resonance<sup>1</sup>: H-3, 6.57; H-4, 6.12; H-5, 6.90; -CH=7.26; -OH, 11.12 (dimethyl sulfoxide); J<sub>3,4</sub> 3.62; J<sub>3,5</sub> 1.50;

 $J_{4.5}$  2.62 c.p.s. It was covered with 1-2 ml of acetic anhydride and shaken until a clear yellow solution was obtained. Ice was added and, after hydrolysis was complete, the solution was neutralized with solid sodium carbonate. After extraction with ether and evaporation the solid was recrystallized from water. The oxime acetate decomposed on attempted purification. Infrared on crude product: NH at 3445, 3460; carbonyl 1765  $cm^{-1}$  and C=N at 1630 cm<sup>-1</sup> (chloroform).

# 2-Acetamidocarbonylpyrrole

In a 3-necked flask was placed 6.75 g silver isocyanate (13) in 5 ml dry benzene. To this was added, with stirring,

and —OH protons ( $\Delta \simeq 3.8$ ) was in agreement with the range suggested for *anti* aldoximes by Kleinspehn *et al.* (12), i.e. about 3.8.

a solution of acetyl chloride (3 g) in 5 ml benzene. The reaction mixture became quite hot and the color darkened somewhat. It was stirred and refluxed for 20 min and cooled to room temperature. Then pyrrole (2.5 g) in 5 ml benzene was added and the mixture refluxed for about an hour, giving a deep green solution. After cooling, the mixture was suction filtered, and the solid washed thoroughly with acetone. All the organic solvent was removed by flash evaporation giving a greenish-black solid. The solid was continuously extracted with boiling water which was then saturated with salt, cooled, and extracted with ether. Evaporation gave a yellow-brown solid which was sublimed and recrystallized to give 0.6 g white crystals m.p. 219-219.5° (11%). This solid was proved to be identical with the high-melting by-product obtained above through the infrared spectrum and mixture melting point.

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