Base- and Acid-catalyzed Condensation Reactions of Reissert Compounds with Vinylpyridines

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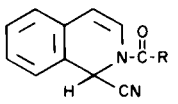
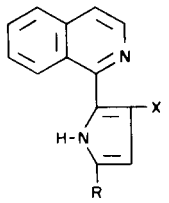
The hydrochloric acid-catalyzed condensation of 2-*p*-anisoyl-1,2-dihydroisoquinaldonitrile (**3**) with 2-vinylpyridine gave 2-(1-isoquinolyl)-3-(2-pyridyl)-5-*p*-anisylpyrrole (**4**), and the corresponding reaction of **3** with 4-vinylpyridine afforded 2-(1-isoquinolyl)-3-(4-pyridyl)-5-*p*-anisylpyrrole (**5**). The condensation of the lithium salt of **3** with 4-vinylpyridine gave α-(4-pyridyl)-β-(1-isoquinolyl)-*p*-methoxypropiophenone (**10**), which was cyclized to 2-(4-pyridyl)-3-*p*-anisylpyrrolo[2,1-*a*]isoquinoline (**7**) by the action of concentrated hydrochloric acid. 2-(4-Pyridyl)-3-phenylpyrrolo[2,1-*a*]isoquinoline (**6**) and 2-(2-pyridyl)-3-*p*-anisylpyrrolo[2,1-*a*]isoquinoline (**8**) were prepared by analogous sequences of reactions.

The hydrochloric acid-catalyzed condensation of 2-benzoyl-1,2-dihydroisoquinaldonitrile (**1**), a typical Reissert compound, with acrylonitrile has been reported (1) to produce 2-(1-isoquinolyl)-3-cyano-5-phenylpyrrole (**2**), the structure of which was established in an unambiguous manner. In view of the known (2) analogy between certain reactions of acrylonitrile and those of 2- or 4-vinylpyridine, we felt that products analogous to **2**, having a 2- or 4-pyridyl group in place of the cyano group, could be produced by acid-catalyzed condensation reactions of Reissert compounds with the latter olefins.



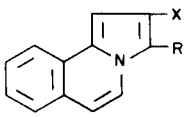
1 (R = phenyl)
3 (R = *p*-anisyl)



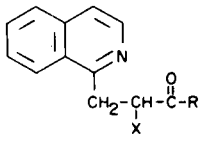
2 (R = phenyl, X = cyano)
4 (R = *p*-anisyl, X = 2-pyridyl)
5 (R = *p*-anisyl, X = 4-pyridyl)

Since there has been recent interest in the analgetic activity of polyarylpyrroles (3), and since a methoxyaryl group is present as a substituent on the pyrrole ring in certain antibiotic compounds having antifungal properties (4), we decided to investigate the reactions of 2-*p*-anisoyl-1,2-dihydroisoquinaldonitrile (**3**), another typical Reissert compound, with 2- and 4-vinylpyridine, respectively. The hydrochloric acid-catalyzed reaction of **3** with 2-vinylpyridine in dioxane solution afforded an insoluble hydrochloride salt of presumably the desired condensation product. Trituration of this salt with sodium hydroxide solution gave a compound of m.p. 185-187°. On the basis of elemental analyses, spectral properties and analogy with the product of the corresponding acrylonitrile reaction, this compound was assigned the structure of 2-(1-isoquinolyl)-3-(2-pyridyl)-5-*p*-anisylpyrrole (**4**). In like manner, a compound of m.p. 213-214°, assumed to be 2-(1-isoquinolyl)-3-(4-pyridyl)-5-*p*-anisylpyrrole (**5**), was obtained by the reaction of **3** with 4-vinylpyridine. The mechanisms of these condensation reactions are thought to be strictly analogous to that proposed (1) previously for the condensation of **1** with acrylonitrile to give **2**.

Reissert compounds may also be used to synthesize substituted pyrrolo[2,1-*a*]isoquinolines, and, in view of recent results of pharmacological interest for compounds containing such ring systems (5), we decided to synthesize 2-(4-pyridyl)-3-phenylpyrrolo[2,1-*a*]isoquinoline (**6**), 2-(4-pyridyl)-3-*p*-anisylpyrrolo[2,1-*a*]isoquinoline (**7**) and 2-(2-pyridyl)-3-*p*-anisylpyrrolo[2,1-*a*]isoquinoline (**8**). The method developed by Boekelheide and Godfrey (6) was used in these syntheses. The condensation of the lithium



6 (R = phenyl, X = 4-pyridyl)
7 (R = *p*-anisyl, X = 4-pyridyl)
8 (R = *p*-anisyl, X = 2-pyridyl)



9 (R = phenyl, X = 4-pyridyl)
10 (R = *p*-anisyl, X = 4-pyridyl)
11 (R = *p*-anisyl, X = 2-pyridyl)

salt of **3** with 4-vinylpyridine in ether-dioxane, for example, gave α-(4-pyridyl)-β-(1-isoquinolyl)-*p*-methoxypropiophenone (**10**), which was then cyclized by the action of concentrated hydrochloric acid to give **7**. Compounds **6** and **8** were obtained in an analogous manner *via* α-(4-pyridyl)-β-(1-isoquinolyl)propiophenone (**9**) and α-(2-pyridyl)-β-(1-isoquinolyl)-*p*-methoxypropiophenone (**11**), respectively (7).

EXPERIMENTAL

2-Benzoyl-1,2-dihydroisoquinaldonitrile (**1**).

This compound was prepared by the method of Weinstock and Boekelheide (8). Recrystallized from ethanol, the product had m.p. 125-127°.

2-*p*-Anisoyl-1,2-dihydroisoquinaldonitrile (**3**).

The method of Popp and Soto (9) was used to prepare this compound. Recrystallized from ethanol, the compound had m.p. 173-174°.

2-(1-Isoquinolyl)-3-(4-pyridyl)-5-*p*-anisylpyrrole (**5**).

To an ice cold solution of 14.50 g. (0.05 mole) of 2-*p*-anisoyl-1,2-dihydroisoquinaldonitrile (**3**) and 5.25 g. (0.05 mole) of 4-vinylpyridine in 150 ml. of freshly distilled dioxane, 50 ml. of concentrated hydrochloric acid solution (36.5%) was added dropwise, with vigorous stirring, over a period of 1 hour. The resulting orange red solution was stirred for 20 additional hours at room temperature. The yellow precipitate which formed was collected by filtration. There was obtained 8.0 g. of a bright yellow solid. By analogy with the product obtained by the reaction of 2-benzoyl-1,2-dihydroisoquinaldonitrile with acrylonitrile, the structure of 2-(1-isoquinolyl)-3-(4-pyridyl-5-*p*-anisylpyrrole hydrochloride was assigned to this product.

The yellow hydrochloride salt was treated with a concentrated solution of sodium hydroxide, and the thick paste which formed was diluted with an excess of water. To the resulting basic mixture a dilute solution of hydrochloric acid was added dropwise until the mixture was neutral, and the yellow solid which precipitated was collected by filtration and thoroughly washed with water. A 5.0 g. quantity of yellow 2-(1-isoquinolyl)-3-(4-pyridyl)-5-*p*-anisylpyrrole (**5**) was obtained, which, after recrystallization from ethanol, melted at 213-214°. The infrared spectrum of this substance taken in chloroform solution showed a characteristic N-H absorption peak at 3460 cm^{-1}.

Anal. Calcd. for $C_{25}H_{19}N_3O$: C, 79.57; H, 5.03; N, 11.14. Found: C, 79.50; H, 4.93; N, 11.15.

2-(1-Isoquinolyl)-3-(2-pyridyl)-5-*p*-anisylpyrrole (**4**).

This reaction was carried out in exactly the same manner as described for the preparation of 2-(1-isoquinolyl)-3-(4-pyridyl)-5-*p*-anisylpyrrole (**5**), with the exception that 2-vinylpyridine was used in place of 4-vinylpyridine. There was obtained 4.3 g. of 2-(1-isoquinolyl)-3-(2-pyridyl)-5-*p*-anisylpyrrole (**4**), which, after recrystallization from ethanol, consisted of a yellow solid melting at 185-187°.

Anal. Calcd. for $C_{25}H_{19}N_3O$: C, 79.57; H, 5.03; N, 11.14. Found: C, 79.50; H, 5.12; N, 10.75.

2-(4-Pyridyl)-3-phenylpyrrolo[2,1-*a*]isoquinoline (**6**).

To a solution of 10.4 g. (0.04 mole) of 2-benzoyl-1,2-dihydroisoquinaldonitrile (**1**) in 150 ml. of anhydrous ether and 75 ml. of anhydrous dioxane, maintained at -10° in an atmosphere of pure nitrogen, was added, with mechanical stirring, an ether-benzene solution of 0.04 mole of phenyllithium. To the resulting deep red solution was added, with stirring, a solution of 12.6 g. (0.12 mole) of 4-vinylpyridine. As the addition progressed, the red color of the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile faded and finally became colorless. The mixture was stirred for an hour at -10° and then was allowed to rise to room temperature and stirred for an additional 17 hours. The reaction mixture was hydrolyzed by addition of 160 ml. of water. The reaction mixture was then added slowly to about 60 g. of Dry Ice, and the mixture was allowed to stand for an hour. The organic layer was separated from the aqueous layer, which was extracted several times with benzene. The combined organic extract was evaporated under reduced pressure in a rotary evaporator. A yellow gum remained as a residue, and this was triturated with hot hexane. This trituration resulted in the formation of a solid, which was collected by filtration. The solid, after having been dried, amounted to 2.8 g. (20.8%) of α-(4-pyridyl)-β-(1-isoquinolyl)propiophenone (**9**), m.p. 188-194°. Two recrystallizations from ethanol gave a white, fluffy solid, m.p. 195-196°. This compound exhibited the characteristic carbonyl absorption peak at 1690 cm^{-1} in its IR spectrum taken in chloroform.

A 1.69 g. (0.005 mole) sample of 2-(4-pyridyl)-β-(1-isoquinolyl)-propiophenone (**9**) and 15 ml. of concentrated sulfuric acid was heated on a steam bath for 30 minutes. The mixture was cooled and poured onto 30 g. of ice. A brown gum which separated was redissolved by addition of dilute hydrochloric acid. Several extractions of the solution with chloroform, carried out until the chloroform extracts were no longer colored, with subsequent concentration of the combined chloroform extract under reduced pressure in a rotary evaporator, gave a yellow gum which was treated with hydrochloric acid. To the resulting solution was added slowly 20 ml. of ethanol containing 1.2 g. of potassium hydroxide, and the solution was heated and filtered hot. The filtrate was cooled and diluted with water, which caused a tan colored solid to precipitate. This was collected by filtration and washed thoroughly with water. The solid amounted to 0.8 g. (50%) of 2-(4-pyridyl)-3-phenylpyrrolo[2,1-*a*]isoquinoline (**6**). Recrystallization from ethanol-water mixture gave tan, needle-like crystals, melting at 151-152°.

Anal. Calcd. for $C_{23}H_{16}N_2$: C, 86.22; H, 5.06; N, 8.74. Found: C, 86.20; H, 5.10; N, 8.60.

2-(4-Pyridyl)-3-*p*-anisylpyrrolo[2,1-*a*]isoquinoline (**7**).

This reaction was carried out in the same manner as that used for the preparation of **9**, with the exception that 0.04 mole of 2-*p*-anisoyl-1,2-dihydroisoquinaldonitrile (**3**) was used in place of **1**. After the extraction with benzene, the combined organic extract was concentrated, leaving solid residue. The solid was collected by filtration and dried. It amounted to 5.2 g. (35.2%) of α-(4-pyridyl)-β-(1-isoquinolyl)-*p*-methoxypropiophenone (**10**), m.p. 178-181°. The infrared spectrum of this compound taken in chloroform exhibited a characteristic carbonyl absorption peak at 1680 cm^{-1}. Recrystallization from ethanol gave white needles melting at 180-181°.

A 1.84 g. (0.005 mole) sample of α-(4-pyridyl)-β-(1-isoquinolyl)-*p*-methoxypropiophenone (**10**) and 20 ml. of concentrated hydrochloric acid was heated on a steam bath for 30 minutes. The mixture was cooled and poured onto 30 g. of ice. Most of the brown gum, which had precipitated, was redissolved by addition of dilute hydrochloric acid. Several extractions of the solution with chloroform, carried out until the chloroform extracts were no longer colored, with subsequent concentration of the combined chloroform extract under reduced pressure in a rotary evaporator, gave

a yellow gum, which was treated with hydrochloric acid. To the resulting solution was added slowly 20 ml. of ethanol containing 1.2 g. of potassium hydroxide, and the solution was heated and filtered hot. The filtrate was cooled and diluted with water, whereupon a yellow colored solid precipitated. This was collected by filtration, washed thoroughly with water and dried. The solid amounted to 1.2 g. (71%) of 2-(4-pyridyl)-3-*p*-anisylpyrrolo[2,1-*a*]-isoquinoline (**7**). Recrystallization from ethanol-water mixture gave yellow needles melting at 187-189°.

Anal. Calcd. for $C_{24}H_{18}N_2O$: C, 82.26; H, 5.18; N, 8.00. Found: C, 82.01; H, 5.41; N, 8.27.

An attempt to bring about the formation of this compound by the use of concentrated sulfuric acid failed to give the desired product. Heating a mixture of 1.84 g. (0.005 mole) of α-(4-pyridyl)-β-(1-isoquinolyl)-*p*-methoxypropiophenone (**10**) and 15 ml. of concentrated sulfuric acid on a steam bath and use of the workup procedure that was employed in the conversion of 2-(4-pyridyl)-β-(1-isoquinolyl)propiophenone (**9**) to 2-(4-pyridyl)-3-phenylpyrrolo-[2,1-*a*]isoquinoline (**6**), gave a yellow solid. This solid did not melt and was very highly soluble in water. Thus, purification posed a problem. Efforts to identify this yellow solid were unsuccessful, but the compound was probably a sulfonic acid.

2-(2-Pyridyl)-3-*p*-anisylpyrrolo[2,1-*a*]isoquinoline (**8**).

This compound, an isomer of 2-(4-pyridyl)-3-*p*-anisylpyrrolo-[2,1-*a*]isoquinoline (**7**), was prepared in an analogous manner from 11.6 g. (0.04 mole) of 2-*p*-anisoyl-1,2-dihydroisoquinaldonitrile (**3**), 0.04 mole of phenyllithium and 12.60 g. (0.12 mole) of 2-vinylpyridine. The workup of the reaction mixture was analogous to that used for the preparation of **10**. The solid isolated amounted to 4.4 g. (30%) of α-(2-pyridyl)-β-(1-isoquinolyl)-*p*-methoxypropiophenone (**11**) m.p. 180-185°. Two recrystallizations from ethanol gave a solid melting at 187-188°.

The procedure used for this cyclization is analogous to that used for the cyclization of α-(4-pyridyl)-β-(1-isoquinolyl)-*p*-methoxypropiophenone (**10**) to 2-(4-pyridyl)-3-*p*-anisylpyrrolo[2,1-*a*]-isoquinoline (**7**). A 1.84 g. (0.005 mole) sample of α-(2-pyridyl)-β-(1-isoquinolyl)-*p*-methoxypropiophenone (**11**) and 20 ml. of concentrated hydrochloric acid yielded a brown solid, which amounted to 1.0 g. (59.2%) of 2-(2-pyridyl)-3-*p*-anisylpyrrolo[2,1-*a*]isoquinoline (**8**) melting at 180-184°. Two recrystallizations from ethanol-water mixture gave brown needles melting at 185-187°.

Anal. Calcd. for $C_{24}H_{18}N_2O$: C, 82.26; H, 5.18; N, 8.00. Found: C, 81.97; H, 5.38; N, 8.29.

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