[CONTRIBUTION FROM THE UNIVERSITY OF NEW MEXICO, LABORATORY OF PHARMACEUTICAL CHEMISTRY]

THE REACTION OF PYRIDINE ALDEHYDES WITH PHENYLACETONITRILES

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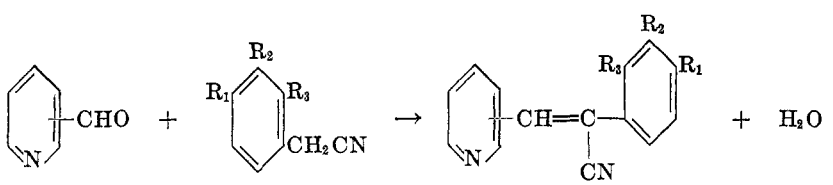
The recent availability of the pyridine aldehydes prompted us to use these compounds as intermediates in the synthesis of potential physiologically active compounds. A series of α-phenyl-β-(2-, 3-, or 4-pyridyl)acrylonitriles was desired as intermediates for the synthesis of analogs of compounds of known physiological activity. However, since this work has been interrupted, the synthesis of the intermediates is reported here.

These substituted acrylonitriles have been prepared from the pyridine aldehydes and the appropriate phenylacetonitrile in the presence of dry methanolic sodium methoxide. This is illustrated in the following equation.



This base-catalyzed condensation of aldehydes with compounds possessing an active methylene group (The Knoevenagel reaction) is well known as a general reaction and has been the subject of many papers, a few of which are indicated by the following references (1–9).

Preliminary screening of the substituted acrylonitriles in rats has not uncovered any significant physiological activity.

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EXPERIMENTAL

All melting points reported are uncorrected. Carbon and hydrogen analyses are by Weiler and Strauss, Oxford.

The pyridine aldehydes were obtained from the Aldrich Chemical Company, Milwaukee, Wisconsin, and were distilled in a vacuum before use. It was necessary to store the aldehydes under dry nitrogen because of ease of oxidation. Phenylacetonitrile was purified by vacuum distillation. The *o*-, and *p*-chlorophenylacetonitriles were prepared from the corresponding benzyl chlorides and were also purified by vacuum distillation. The 3,4-dimethoxyphenylacetonitrile was obtained from Eastman Kodak Company and was used without further purification.

The preparation of the substituted acrylonitriles recorded in Table I is illustrated by the following procedure. This is essentially the procedure employed by Rorig (10).

α-Phenyl-β-(3-pyridyl)acrylonitrile. To a solution of 2.34 g. (0.02 mole) of phenylacetonitrile and 2.14 g. (0.02 mole) of nicotinaldehyde in 40 ml. of absolute methanol at 50–60°

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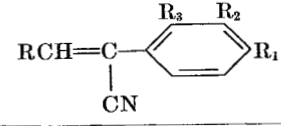
TABLE I

α-PHENYL-β-(2-, 3-, OR 4-PYRIDYL)ACRYLONITRILES



Substituents				Formula	Yield,[a] %	M.P.,°C. uncorr.	Color	Analyses			
								Carbon		Hydrogen	
R	R_1	R_2	R_3					Calc'd	Found	Calc'd	Found
4-Pyridyl-	H	H	H	$C_{14}H_{10}N_2$	30	128–129	White	81.53	81.30	4.89	5.14
3-Pyridyl-	H	H	H	$C_{14}H_{10}N_2$	42	92	White	81.53	81.54	4.89	4.81
2-Pyridyl-	H	H	H	$C_{14}H_{10}N_2$	55	65	White	81.53	80.66[b]	4.89	4.68
4-Pyridyl-	OCH_3	OCH_3	H	$C_{16}H_{14}N_2O_2$	64	138.5–139.5	White	72.16	72.12	5.30	5.38
3-Pyridyl-	OCH_3	OCH_3	H	$C_{16}H_{14}N_2O_2$	83	141–142	Faintly yellow-green	72.16	71.83	5.30	5.13
2-Pyridyl-	OCH_3	OCH_3	H	$C_{16}H_{14}N_2O_2$	75	110–111	Pale yellow	72.16	72.35	5.30	5.10
4-Pyridyl-	Cl	H	H	$C_{14}H_9ClN_2$	91	138.5–139.5	White	69.86	69.40	3.77	3.57
3-Pyridyl-	Cl	H	H	$C_{14}H_9ClN_2$	95	138–139	White	69.86	70.13	3.77	3.75
2-Pyridyl-	Cl	H	H	$C_{14}H_9ClN_2$	91	124.5–125.5	White	69.86	70.07	3.77	3.93
3-Pyridyl-	H	H	Cl	$C_{14}H_9ClN_2$	86	112–113	White	69.86	69.30	3.77	3.77

[a] Yield of unrecrystallized product. [b] Even after repeated purification, consistently low carbon values were obtained.

was added 0.4 g. of finely powdered sodium methoxide. The solution immediately became yellow, then orange. The temperature was maintained for five to ten minutes and then the reaction mixture was allowed to come to room temperature and stand for at least one hour. Upon cooling in an ice-bath, a nearly white precipitate separated, which upon filtration and drying amounted to 1.73 g. (42%), m.p. 85–88°. After two crystallizations from aqueous ethanol, the compound melted at 92°.

In some instances it was necessary to decolorize the compounds with Norit. It was not uncommon to crystallize some of these compounds five to six times to obtain analytically pure specimens. Even so, some of the compounds prepared did not yield analytically pure specimens.

The condensation products from both pyridine 2-aldehyde and pyridine 4-aldehyde with *o*-chlorophenylacetonitrile even after repeated purification gave carbon analyses consistently 2% low. The three pyridine aldehydes were also condensed with α-naphthylacetonitrile from which only deep red oils were isolated. With 2-cyanomethyl-4,4-dimethyl-1-isopropylimidazoline, the three pyridine aldehydes gave solid condensation products, but these even after repeated crystallization, gave carbon values as much as 6% low.

SUMMARY

Ten substituted α-phenyl-β-(2-, 3-, or 4-pyridyl)acetonitriles have been prepared. These compounds possess no significant physiological activity after preliminary screening. These compounds have not previously been recorded in the literature.

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