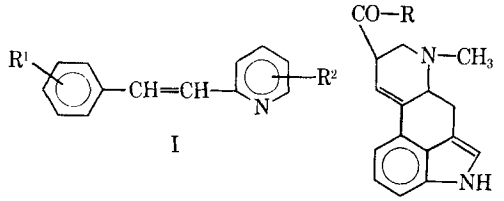
New Compounds: Pyridylacrylonitrile Derivatives

By JOSEPH SAM*

The preparation of several pyridylacrylonitriles (V), the hydrolysis to an acid (VII), and subsequent conversion to an ester (VIII) are described.

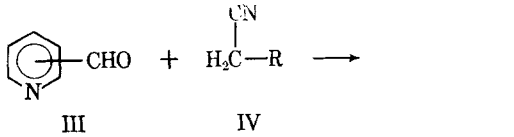
THE AVAILABILITY of pyridinealdehydes prompted the investigation of a number of their derivatives for potentially useful biological agents. Others (1–9) have described the preparation of similar compounds. Substituted 2-stilbazoles (I) or the corresponding hydrogenated derivatives bear some structural similarity to the ergot (II), veratrum, and reserpine alkaloids and also to the synthetic and steroidal estrogens. The nitriles (V) also have some structural similarity to the ergot alkaloids.



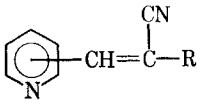
I

II

The reaction of pyridinealdehydes (III) with substituted acetonitriles (IV) was catalyzed by piperidine and provided yields of 64 to 96% of the desired acrylonitriles (V). (Scheme I.)



III IV



V

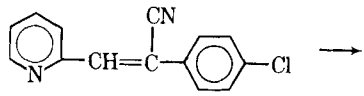
Scheme I

The hydrolysis of 2-(*p*-chlorophenyl)-3-(2-pyridyl)acrylonitrile (VI) with concentrated sulfuric acid provided the corresponding acid (VII) which was subsequently reacted with ethanolic hydrogen chloride to yield the ester (VIII). (Scheme II.)

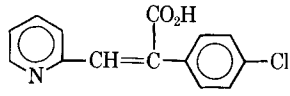
On the basis of the successful reductive cyclization of α-(2′-nitro-4′,5′-dimethoxyphenyl)-β-phenylacrylonitrile (IX) to 3-benzyl-5,6-dimethoxyindole (X) (6) (Scheme III), a number of unsuccessful attempts were made to cyclize β-cyano-4′,5′-dimethoxy-2′-nitro-2-stilbazole (XI) to 5,6-dimethoxy-3-(2-pyridylmethyl)indole (XII) by the same procedure. (Scheme IV.)

The reductive cyclization of XI to 3-cyano-2-(pyridyl)indoles (XIII) has been reported (7).

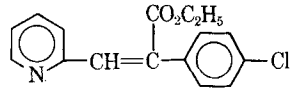
Table I summarizes the physical characteristics of the compounds that were investigated.



VI

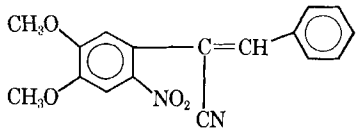


VII

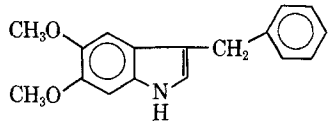


VIII

Scheme II

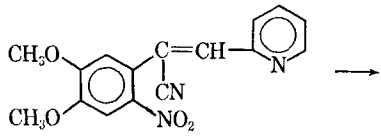


IX

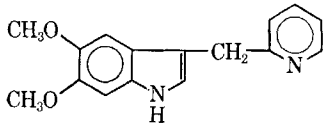


X

Scheme III

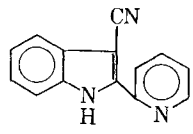


XI



XII

Scheme IV



XIII

Preliminary pharmacological evaluation did not indicate any pronounced biological activity in the compounds that were studied.

EXPERIMENTAL[1]

Synthesis—The starting materials for the preparation of the compounds described in Table I (with

Received March 30, 1967, from Bristol Laboratories' Syracuse, NY 13201
Accepted for publication June 7, 1967.
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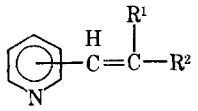
[1] All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected.

TABLE I—PYRIDYLACRYLONITRILE DERIVATIVES



Pyridyl Isomer	R^1	R^2	% Yield	Recrystn. Solvent[a]	M.p., °C.	Molecular Formula	Anal. Calcd. C	Calcd. H	Found C	Found H
2	3,4-$(CH_3O)_2$-6-$NO_2C_6H_2$	CN	96	EA	192.5–193.5	$C_{16}H_{13}N_3O_4$	61.7	4.21	62.0	4.28
2	4-$NO_2C_6H_4$	CN	96	M	199–201	$C_{14}H_8N_3O_2$[b]	66.9	3.61	67.1	3.70
2	4-ClC_6H_4	CN	67	M	128–129	$C_{14}H_9ClN_2$	69.9	3.77	69.9	3.81
2	4-ClC_6H_4	CO_2H	90	B	147–148 dec.	$C_{14}H_{10}ClNO_2$	64.8	3.88	64.9	3.86
2	4-ClC_6H_4	$CO_2C_2H_5$	90	A	140–142	$C_{17}H_{17}ClINO_2$[c]	47.5	3.99	47.4	4.19
2	4-ClC_6H_4	$CO_2C_2H_5$	86	E	134–135	$C_{16}H_{14}ClNO_2$	66.8	4.90	67.0	5.19
2	$C_2H_5O_2C$	CN	64	M	94.5–96	$C_{11}H_{10}N_2O_2$[d]	65.3	4.99	65.5	4.87
3	$C_2H_5O_2C$	CN	83	M	87.5–88.5	$C_{11}H_{10}N_2O_2$	65.3	4.99	65.2	4.74

[a] EA, ethyl acetate; M, methanol; B, benzene; A, acetone; E, ethanol. [b] *Reference 8.* [c] Methiodide. [d] *Reference 9.*

the exception of 3,4-dimethoxy-6-nitrophenylacetonitrile) were purchased from commercial sources. The latter nitrile was prepared according to the procedure described in the literature (6).

Pyridylacrylonitriles (Table I)—A cooled solution of 0.1 mole of desired nitrile and 0.1 mole of pyridinealdehyde in 100–150 ml. of absolute ethanol or methanol was treated with 8.5 Gm. (0.1 mole) of piperidine and thereafter refluxed for 1–5 hr. The solution was concentrated to a small volume. The solid was removed by filtration and recrystallized from a suitable solvent.

α-(p-Chlorophenyl)-β-(2-pyridyl)acrylic Acid—A carefully prepared solution of 7 Gm. (0.03 mole) of α-(*p*-chlorophenyl)-β-(2-pyridyl)acrylonitrile in 100 Gm. of concentrated sulfuric acid was heated on a steam bath for 0.5 hr. Thereafter, the solution was cooled and poured into 500 ml. of water. The solid (7 Gm., 90%) was removed by filtration and dissolved in 10% aqueous sodium hydroxide. The resulting solution was filtered and the filtrate was neutralized with acetic acid. The solid was removed by filtration and recrystallized from benzene, m.p. 147–148° dec.

Ethyl α-(p-Chlorophenyl)-β-(2-pyridyl)acrylate—A solution of 50 Gm. of hydrogen chloride in 200 ml. of absolute ethanol was treated with 26 Gm. (0.1 mole) of α-(*p*-chlorophenyl)-β-(2-pyridyl)acrylic acid. The resulting solution was refluxed for 4 hr. and thereafter concentrated *in vacuo* to dryness. The residual material was washed with 300 ml. of water and recrystallized from ethanol.

A methiodide was prepared by refluxing the compound above with excess methyl iodide in acetonitrile for 30 hr.

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